

The role of nutrition and nutraceutical supplements in the prevention and treatment of hypertension



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Practice Points

- Vascular biology (endothelial and vascular smooth muscle dysfunction) play a primary role in hypertension.
- Nutrition (i.e., natural whole food and nutraceuticals) alter blood pressure by various vascular biology mechanisms.
- Oxidative stress, inflammation and immune dysfunction of the arteries are the finite response in hypertension.
- Antioxidants can prevent and treat hypertension.

SUMMARY Macronutrient and micronutrient deficiencies are frequently found in subjects with cardiac disease, vascular problems, hypertension and dyslipidemia as a result of genetic–environmental interactions, and prescription and over-the-counter drug use. The impact on cardiovascular outcomes and healthcare costs is large. The diagnosis and treatment of these nutrient deficiencies may improve endothelial dysfunction and vascular disease and lower blood pressure. Vascular biology with endothelial activation, inflammation oxidative stress and immune dysfunction of arteries are early events in hypertension-related vascular disease. Proper nutrition, nutraceuticals, vitamins, weight management, exercise and other lifestyle changes, are effective in the management of hypertension in most patients. A combination of drugs with these lifestyle treatments reduce cardiovascular disease. The new scientific role for nutraceuticals and nutrition in the treatment of essential hypertension are reviewed in this article.

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Hypertension is a disease of the arteries caused by interactions of genes, environment and nutrients that induce oxidative stress, inflammation and immune vascular dysfunction. There are an infinite number of insults to the vascular system but only these three finite responses. Alteration of the nutrient gene interaction has the potential to reduce blood pressure (BP) and cardiovascular disease [1].

The Paleolithic diet, in contrast to the modern diet, has resulted in many nutritionally related diseases such as hypertension, dyslipidemia, metabolic syndrome, diabetes mellitus (DM), obesity, atherosclerosis, coronary heart disease (CHD), myocardial infarction (MI), congestive heart failure (CHF), cerebrovascular accidents (CVAs), and renal disease [1,2]. Optimal nutrition and specific nutraceutical supplements results in reduction in inflammation, oxidative stress, vascular autoimmune dysfunction and postprandial endotoxemia with intermediate and long-term improvements in cardiovascular and CHD morbidity and mortality [1-4].

Nutrition & disease prevention

A more logical approach to lower BP and cardiovascular disease (CVD) is to integrate lifestyle changes, proper nutrition, scientifically proven nutraceuticals and drugs [1-6]. This approach will reduce the need for drugs, decrease drug costs and adverse effects while delaying or preventing hypertension and related target organ damage. The primary mechanism of action is to reduce inflammation, oxidative stress and immune dysfunction in the vascular system [1,7,8].

Approximately 50% of patients with hypertension will respond to the above nondrug treatments, but an assessment of BP level and the presence of clinical target organ damage, diabetes mellitus, clinical CVD or significant risk factors must be evaluated [5,7]. Depending on these factors, it is reasonable to treat with a nonpharmacologic approach for approximately 6 months prior to starting drug therapy.

Hypertension, oxidative stress, inflammation & autoimmune dysfunction in the vascular system in humans

Oxidative stress, inflammation and autoimmune dysfunction of the vascular system are the primary pathophysiological and functional mechanisms that induce vascular

disease [3,4,6,9-25]. All three of these are closely inter-related and establish a deadly combination that leads to endothelial dysfunction, vascular smooth muscle dysfunction, hypertension, vascular disease, atherosclerosis and CVD.

Oxidative stress, with an imbalance between radical oxygen species (ROS) and the antioxidant defense mechanisms, contributes to the etiology of hypertension in animals [9] and humans [6,10]. ROS are generated by multiple cellular sources, including NADPH oxidase, mitochondria, xanthine oxidase, uncoupled endothelium-derived NO synthase, cyclo-oxygenase and lipo-oxygenase [6]. Superoxide anion is the predominant ROS species produced by these tissues. Hypertensive patients have impaired endogenous and exogenous antioxidant defense mechanisms [11], an increased plasma oxidative stress and an exaggerated oxidative stress response to various stimuli [11,12]. Hypertensive subjects also have lower plasma ferric reducing ability of plasma, lower vitamin C levels and increased plasma 8-isoprostanes, which correlate with both systolic and diastolic BP. Various single-nucleotide polymorphisms (SNPs) in genes that code for antioxidant enzymes, are directly related to hypertension [20]. These include NADPH oxidase, xanthine oxidase, SOD 3 (superoxide dismutase), catalase, GPx 1 (glutathione peroxidase) and thioredoxin. Numerous epidemiologic, observational and interventional studies have demonstrated increase ROS production and reduced oxidative defense in hypertension in humans [11-13]. ROS directly damage endothelial cells, degrade NO, influence eicosanoid metabolism, oxidize LDL, lipids, proteins, carbohydrates, DNA and organic molecules, increase catecholamines, damage the genetic machinery, and influence gene expression and transcription factors. The increased oxidative stress, inflammation and autoimmune vascular dysfunction is implicated in human hypertension **Figure 1** [11-15].

The link between inflammation and hypertension has been suggested in both cross-sectional and longitudinal studies [16]. Increases in high-sensitivity CRP (HS-CRP) as well as other inflammatory cytokines occur in hypertension and hypertensive-related target organ damage, such as increased carotid intima-media thickness (IMT) [17]. HS-CRP predicts future cardiovascular events [16,17]. Elevated HS-CRP is both a risk marker and risk factor

for hypertension and CVD [21,22]. Increases in HS-CRP of over 3 µg/ml may increase BP in just a few days, which is directly proportional to the increase in HS-CRP [21,22]. Nitric oxide (NO) and eNOS are inhibited by high sensitivity CRP [21,22]. The angiotensin type 2 receptor (AT2R), which normally counterbalances the angiotensin type 1 receptor (AT1R), is downregulated by HS-CRP [21,22]. Angiotensin II (A-II) upregulates many of the cytokines, especially IL-6, cell adhesion molecules (CAMs) and chemokines by NF-κB leading to vasoconstriction. These events, along with the increases in oxidative stress and endothelin-1, elevate BP [16].

Activation of the immune system, both innate and adaptive responses, is also linked to hypertension and hypertension-induced CVD through at least three mechanisms: cytokine production, CNS stimulation and renal damage [18–25]. This includes salt-sensitive hypertension with increased renal inflammation as a result of T cell imbalance, dysregulation of CD4⁺ and CD8⁺ lymphocytes and chronic leukocytosis with increased neutrophils and reduced lymphocytes [18,19,23]. Macrophages and various T-cell subtypes regulate BP, invade the arterial wall, activate Toll-like receptors and induce autoimmune vascular damage [24]. A-II activates immune cells (T cells, macrophages and dendritic cells) and promotes cell infiltration into target organs [24]. CD4⁺ T lymphocytes express AT1R and PPAR-γ receptors, when activated, release TNF-α, interferon and interleukins within the vascular wall [24]. IL-17 produced by T cells may play a pivotal role in the genesis of hypertension caused by A-II [24].

Evolutionary nutrition

The human genome is 99.9% that of our Paleolithic ancestors, yet our nutritional intake is completely different [2]. The nutritional variations, ROS, inflammatory mediators, CAMs, signaling molecules and autoimmune dysfunction induce CVD and hypertension by environment, nutrition and genetic interactions and nutrient-caveolae interactions in the endothelium [3,4,26,27]. Reduction in NO bioavailability and endothelial activation initiate the vascular dysfunction and hypertension. Increased sodium intake, lower potassium intake, decreased ω-3 fatty acid intake, higher *trans* fat and saturated fat intake, improper nutrition, obesity and reduced exercise have

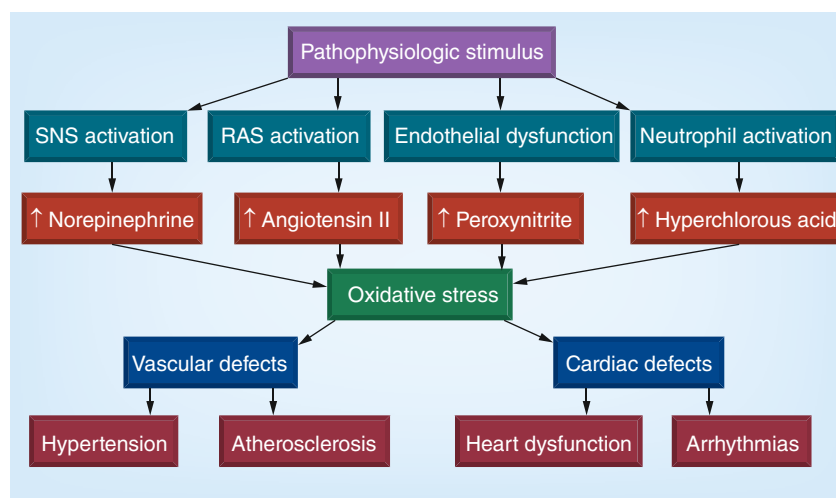


Figure 1. Neurohormonal and oxidative stress system interaction on cardiac and vascular muscle.

resulted in a significant increase in nutritionally related diseases, and increased the incidence of hypertension and CVD [3,4,2,28,29].

Sodium (Na⁺)

Increased sodium intake is associated with higher BP and dietary sodium reduction lowers BP (Table 1) [30–32]. Sodium directly increases heart disease, stroke and renal disease independent of BP [33,34]. Sodium increased platelet reactivity, sympathetic nervous system activity through both central and noncentral mechanisms, stroke (independent of BP), left ventricular hypertrophy, diastolic dysfunction, vascular hypertrophy, MI, CHF sudden death and left ventricular filling pressures [33,34]. The renal plasma flow falls and there is an increase in glomerular filtration rate and intraglomerular capillary pressure. This results in microalbuminuria, proteinuria and renal insufficiency and arterial stiffness [33,34], especially in salt-sensitive hypertensive patients [35,36].

Sodium increases endothelial cell stiffness, reduces size, surface area, volume, cytoskeleton, deformability and pliability, reduces eNOS and NO production, increases asymmetric dimethylarginine (ADMA), increases oxidative stress, induces an imbalance of NO and A-II, and increases TGF-β. Potassium counteracts all of the actions of sodium [37–42]. High sodium intake abolishes the AT2R-mediated vasodilation immediately by decreasing the level of AT2R protein [43]. After 30 days there is complete abolition of endothelial vasodilation [43]. Endothelial cells act as vascular salt sensors [42].

Table 1. Nutritional recommendations.

Nutrition	Daily intake
▪ DASH I, DASH II-Na ⁺ and PREMIER diets	–
▪ Sodium restriction	1500 mg
▪ Potassium	4700 mg
▪ Potassium:sodium intake ratio >3:1	–
▪ Magnesium	1000 mg
▪ Zinc	50 mg
▪ Protein (total intake; 30% total calories):	1.5–1.8 g/kg
▪ Nonanimal sources, organic lean or wild animal protein	–
▪ Whey protein	30 g
▪ Soy protein	30 g
▪ Sardine muscle concentrate extract	3 mg
▪ Cold water fish, fowl poultry	–
▪ Milk peptides	30–60 mg
▪ Fats (30% total calories):	
▪ ω-3 fatty acids PUFA (DHA, EPA, cold water fish)	2–3 g
▪ ω-6 fatty acids PUFA (canola oil, nuts)	1 g
▪ ω-9 fatty acids MUFA (extra virgin olive oil, olives)	2–4 tablespoons or 5–10 olives
▪ Saturated FA (lean, wild animal meat) (30%)	<10% total calories
▪ P:S ratio >2.0	–
▪ ω-3/ω-6 PUFA, ratio 1:1–1:2	–
▪ No transfatty acids (0%; hydrogenated margarines, vegetable oils)	–
▪ Nuts: e.g., almonds, walnuts, hazelnuts	–
▪ Carbohydrates (40% total calories):	
▪ Reduce or eliminate refined sugars and simple carbohydrates	–
▪ Increase complex carbohydrates and fiber, whole grains (oat, barley, wheat), vegetables, beans, legumes	
– oatmeal or	60 g
– oatbran (dry) or	40 g
– β-glucan or	3 g
– psyllium	7 g
▪ Garlic	4 cloves/4 g aged garlic 600 mg b.i.d.
▪ Wakame seaweed (dried)	3.0–3.5 gram
▪ Lycopene	10–20 mg
▪ Tomatoes and tomato products, supplements or	
▪ guava, watermelon, apricots, pink grapefruit, papaya	
▪ Dark chocolate	100 g
▪ Sesame	60 mg sesamin or 2.5 g sesame meal

b.i.d.: Twice a day; DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; FA: Fatty acid; MUFA: Monounsaturated fatty acid; P:S: Polyunsaturated:saturated fats; PUFA: Polyunsaturated fatty acid.

Reduction of dietary sodium reduces CVD that is both dependent and independent of BP [33,34]. A balance of sodium with potassium and magnesium lowers BP and CVD [28,37,38,44]. Sodium intake per day in hypertensive patients

should be between 1500 and 2000 mg. Sodium restriction improves BP reduction in those patients that are receiving pharmacologic treatment [37,38].

Potassium (K⁺)

Dietary K⁺ should be 4700 mg day (120 mmol) with a K⁺:Na⁺ ratio of approximately 4–5:1 [28,45]. An increase in dietary K⁺ intake will lower BP in both normotensive and hypertensive patients [28,45,46]. The average BP reduction with a K⁺ supplementation of 4700 mg per day is 4.4/2.5 mmHg in hypertensive subjects but may be as much as 8/4.1 mmHg with 120 mmol per day (4700 mg) [28,45,46]. The response depends on race (higher in black than white patients), sodium, magnesium and calcium intake [28]. Those on a higher sodium intake have a greater reduction in BP with potassium [28]. Potassium lowers the incidence of cardiovascular and CVAs independent of the BP reduction [28–47]. There are also reductions in CHF, left ventricular hypertrophy, DM and cardiac arrhythmias [28]. If the serum potassium falls below 4.0 meq/dl there is an increased risk of CVD mortality, ventricular tachycardia, ventricular fibrillation and CHF [28]. Red blood cell potassium is a better indication of total body stores and thus, CVD risk than serum potassium [28].

Potassium increases natriuresis, modulates baroreflex sensitivity, vasodilates, decreases sensitivity to catecholamines and A-II, and increases sodium potassium ATPase and DNA synthesis in the vascular smooth muscle cells and sympathetic nervous system cells, resulting in improved function [28]. In addition, potassium increases bradykinin and urinary kallikrein, decreases NADPH oxidase, which lowers oxidative stress and inflammation, improves insulin sensitivity, decreases ADMA, reduces intracellular sodium and lowers production of TGF-β [28].

It is estimated that each 1000 mg increase in potassium intake per day will reduce all-cause mortality by 20% and each 1000 mg decrease in sodium intake per day will decrease all-cause mortality by 20% [44]. It is recommended that patients consume 4.7 g of potassium per day through dietary means and reduce sodium to less than 1500 mg per day [28]. Potassium in food or from supplementation should be reduced or used with caution in those patients with renal

impairment or those on medications that increase renal potassium retention [28].

Magnesium (Mg^{2+})

There is an inverse relationship between dietary magnesium intake and BP [45,48,49]. The maximum reduction in clinical trials has been 5.6/2.8 mmHg but some studies have shown no change in BP [50]. The combination of high potassium and low sodium intake with increased magnesium intake had additive antihypertensive effects with and without drugs [50].

Magnesium acts like a calcium channel blocker (CCB), increases prostaglandin E, NO, endothelial function works with potassium, to lower systemic vascular resistance (SVR) and BP [45,48–50].

Intracellular level of magnesium (red blood cell) is more indicative of total body stores and should be measured in conjunction with serum and urinary magnesium [50]. It is recommended that magnesium is taken in doses of 500–1000 mg per day of a chelated magnesium (chelated to an amino acid) to improve absorption and decrease the incidence of diarrhea [50]. Adding taurine at 1000–2000 mg per day will enhance the antihypertensive effects of magnesium [50]. Magnesium supplements should be avoided or used with caution in patients with known renal insufficiency or in those taking medications that induce magnesium retention [50].

Calcium (Ca^{2+})

Calcium supplementation is not recommended at this time as an effective means to reduce BP as studies are inconsistent and BP reductions are minimal [45,51,52].

Zinc (Zn^{2+})

Low serum zinc levels are associated with hypertension and CHD [53,54]. Zinc is transported into cardiac and vascular muscle and other tissues by metallothionein [55]. Genetic deficiencies of metallothionein with intramuscular zinc deficiencies may lead to increased oxidative stress, mitochondrial dysfunction, cardiomyocyte dysfunction and apoptosis with subsequent myocardial fibrosis, abnormal cardiac remodeling, heart disease, heart failure or hypertension [55]. Intracellular calcium increases oxidative stress, which is reduced by zinc [55]. Zinc intake should be 50 mg per day through either diet or supplements [1].

Protein

High protein intake, from both vegetable and animal sources reduces BP [56–59]. In the Intersalt study of over 10,000 subjects, those with a dietary protein intake 30% above the mean had a lower BP by 3.0/2.5 mmHg compared with those that were 30% below the mean (81 vs 44 g per day) [56]. The content of various types of fat in the protein alters the BP response [56,59]. A meta-analysis confirmed these findings and also suggested that hypertensive patients and the elderly have the greatest BP reduction with protein intake [57]. A randomized crossover study in 352 adults with prehypertension and stage I hypertension found a significant reduction in systolic blood pressure (SBP) of 2.0 mmHg with soy protein and 2.3 mmHg with milk protein compared with a high glycemic index diet over each of the 8-week treatment periods [60]. There was a nonsignificant reduction in diastolic blood pressure (DBP). The recommended intake of protein from all sources is 1.0–1.5 g per kg per day depending on exercise level, age, renal function and other factors [1,37,38].

Fermented milk and whey protein concentrate 20 g per day significantly reduces BP in human studies by 8/2 mmHg [61–66]. Milk peptides, which contain both caseins and whey proteins, are a rich source of angiotensin converting enzyme inhibitor (ACEI) peptides. Val-Pro-Pro and Ile-Pro-Pro given at 5–60 mg per day have variable reductions in BP with an average decrease in pooled studies of approximately 4.8/2.2 mmHg [38,61,63–65]. However a recent meta-analysis did not show significant reductions in BP in humans [65].

Marine collagen peptides from deep sea fish have antihypertensive activity [67–69]. A double-blind placebo-controlled trial in 100 hypertensive subjects with diabetes who received Marine collagen peptides twice a day for 3 months had significant reductions in DBP and mean arterial pressure [67]. Bonito protein (*Sarda orientalis*), from the tuna and mackerel family has natural ACEI inhibitory peptides and reduces BP 10.2/7 mmHg at 1.5 g per day [METAGENICS RESEARCH CORP., PERS. COMM.] [68]. These are recommended.

Sardine muscle protein at 3 mg a day (Valyl-Tyrosine), significantly lowers BP by 9.7/5.3 mmHg in hypertensive subjects [70,71]. These are recommended.

Soy protein intake was significantly and inversely associated with both SBP and DBP in 45,694 Chinese women consuming 25 g per day or more of soy protein over 3 years, and the association increased with age [72]. The SBP reduction was 1.9–4.9 mm lower and the DBP was 0.9–2.2 mmHg lower [72]. However, randomized clinical trials and meta-analysis have shown mixed results on BP with no change in BP to reductions of 7 to 10% for SBP and DBP [73–77]. Some studies suggest improvement in endothelial function, improved arterial compliance, reduction in HS-CRP and inflammation, ACEI activity, reduction in sympathetic tone, diuretic action and reduction in both oxidative stress and aldosterone levels [76,78,79]. Fermented soy at approximately 25 g per day is recommended.

Fats

The clinical effect of fats on BP are inconsistent [80,81]. The best data on BP reduction is with ω -3 fatty acids and less so with monounsaturated fatty acids.

ω -3 polyunsaturated fatty acids

ω -3 polyunsaturated fatty acids significantly lower BP in human trials [82–86].

Docosahexaenoic acid (DHA) is more effective in reducing BP and heart rate than eicosapentaenoic acid (EPA) [82]. The average reduction in BP is 8/5 mmHg and heart rate falls approximately 6 bpm [1,37,38,82,87–89]. However, formation of EPA and ultimately DHA from α -lipoic acid (ALA) is very small and usually less than 5% [1]. In patients with chronic kidney disease, 4 g of ω -3 fatty acids reduced BP measured with 24 h ambulatory blood pressure (ABM) over 8 weeks by 3.3/2.9 mmHg compared with placebo ($p < 0.0001$) [2,84].

ω -3 fatty acids (FAs) have been shown to increase eNOS and NO, improve in endothelial dysfunction, reduce plasma norepinephrine and increase parasympathetic nervous system tone, suppress ACE activity and improve insulin resistance [90]. The recommended daily dose is 3000–5000 mg per day of combined DHA and EPA in a ratio of 2:3 and approximately 50% of this dose as GLA combined with γ/δ tocopherol at 100 mg per g of DHA and EPA to get the ω -3 index of 8% or higher to reduce BP and provide optimal cardioprotection [91].

ω -9 FA

Olive oil, a monounsaturated fatty acid (MUFA), lowers BP [92,93]. Olive oil and monounsaturated fats have shown consistent reductions in BP in most clinical studies in humans [92–97]. In one study, the SBP fell by 8 mmHg ($p \leq 0.05$) and the DBP fell by 6 mmHg ($p \leq 0.01$) in both clinic and 24-h ambulatory BP monitoring on monounsaturated fats [92]. Extra virgin olive oil was more effective than sunflower oil in lowering SBP in a group of 31 elderly hypertensive patients in a double-blind randomized crossover study [94]. The SBP was 136 mmHg in the extra virgin olive oil treated subjects versus 150 mmHg in the sunflower-treated group ($p < 0.01$). Olive oil also reduces BP in hypertensive diabetic subjects [95]. Olive leaf extract at 500 mg twice a day reduced BP in stage I hypertensive patients over 8 weeks by 11.5/4.8 mmHg, which was equivalent to captopril 25 mg twice a day [97].

Fiber

Increased fiber intake to reduce BP has been inconsistent in clinical studies [1,37,38,98,99]. The average reduction in BP is approximately 7.5/5.5 mmHg on 40–50 g per day of a mixed fiber [37,38,98,99]. There is improvement in insulin sensitivity, endothelial function, reduction in sympathetic nervous system activity and an increase in renal sodium loss [1,37,38,98].

Garlic

Garlic lowers BP by approximately 8.4/7.3 mmHg in meta-analysis reviews [100,101]. Aged garlic, cultivated garlic (*Allium sativum*), wild uncultivated garlic or bear garlic (*Allium ursinum*), aged or fresh garlic have variable effects [1,37,38,100,101]. Garlic is also effective in reducing BP in patients with uncontrolled hypertension who are already on antihypertensive medication [102]. In a double-blind parallel randomized placebo-controlled trial of 50 patients, 900 mg of aged garlic extract with 2.4 mg of S-allylcysteine was administered daily for 12 weeks and reduced SBP 10.2 mmHg ($p = 0.03$) more than the control group in those with SBP over 140 mmHg [102]. Since the results are highly variable, better developed studies are needed before clear recommendations are made.

Garlic has ACEI activity, calcium channel blocking activity, reduces catecholamine sensitivity, improves arterial compliance, increases bradykinin and NO, and contains

adenosine, magnesium, flavonoids, sulfur, allicin and phosphorus that reduce BP [1,37,38].

Tea: green & black

The effects of chronic green or black tea consumption on BP are inconsistent in humans [103–106].

Seaweed

Wakame seaweed (a natural food, not a supplement) at 3.3 g of dried wakame for 1 month lowered BP 14/5 mmHg [107]. In a study men with mild hypertension given a seaweed preparation, mean arterial pressure fell by 11.2 mmHg ($p < 0.001$) [108].

Seaweed and sea vegetables contain 77 minerals, fiber and alginate in a colloidal form [107–109]. Wakame contains ACEI from various amino acid peptides [109–111].

Vitamin C

Vitamin C or plasma ascorbate concentration in humans is inversely correlated to BP and heart rate [112–126] and a reduced risk of CVD and CVA [115].

An evaluation of the published clinical trials indicates that vitamin C dosing at 250 mg twice daily will lower BP by approximately 7/4 mmHg [112–126]. Vitamin C will induce a sodium water diuresis, improve arterial compliance, improve endothelial function, increase NO and PGI₂, decrease adrenal steroid production, improve sympathovagal balance, increase red blood cell Na/K ATPase, increase superoxide dismutase, improve aortic elasticity and compliance, improve flow-mediated vasodilation, decrease pulse wave velocity and augmentation index, increase cyclic GMP, activate potassium channels, reduce cytosolic calcium and reduce serum aldehydes [124]. Vitamin C improves the efficacy of amlodipine, decreases the binding affinity of the AT₁R by A-II by disrupting the AT₁R disulfide bridges and lowers BP in the elderly with refractory hypertension [1,37,38,116–121]. In elderly patients with refractory hypertension already on maximum pharmacologic therapy, 600 mg of vitamin C daily lowered BP by 20/16 mmHg [121]. A serum level of 100 $\mu\text{mol/l}$ is recommended [1,37,38]. A depletion–repletion study of vitamin C demonstrated an inverse correlation of plasma ascorbate levels, SBP and DBP [122]. In a meta-analysis of 13 clinical trials with 284 patients, vitamin C at 500 mg per day

over 6 weeks reduced SBP by 3.9 mmHg and DBP by 2.1 mmHg [123].

There is an inverse relationship to vitamin C intake and plasma ascorbate levels [112–126]. Hypertensive subjects were found to have significantly lower plasma ascorbate levels compared with normotensive subjects (40 vs 57 $\mu\text{mol/l}$ respectively) [127]. Vitamin C may be obtained at this dose in food or with supplements.

Vitamin E

The relationship of vitamin E and BP has been very inconsistent, but most studies have not shown reductions in BP with most forms of tocopherols or tocotrienols [1,37,38]. Patients with Type 2 DM and controlled hypertension (130/76 mmHg) on prescription medications, with an average BP of 136/76 mmHg, were administered mixed tocopherols containing 60% γ -, 25% δ - and 15% α -tocopherols [128]. The BP actually increased by 6.8/3.6 mmHg in the study patients ($p < 0.0001$) but was less than the increase with α -tocopherol of 7/5.3 mmHg ($p < 0.0001$). γ -tocopherol may have natriuretic effects by inhibition of the 70-pS potassium channel in the thick ascending limb of the loop of Henle and lower BP [129]. Both α - and γ -tocopherol improve insulin sensitivity and enhance adiponectin expression via PPAR- γ -dependent processes, which have the potential to lower BP and serum glucose [130]. Vitamin E is not recommended for BP treatment in supplement form but may be beneficial in other diseases.

Vitamin D

The plasma levels of Vitamin D₃ are associated with BP [131–142]. Vitamin D₃ regulates the renin–angiotensin–aldosterone system [132]. If the Vitamin D level is below 30 ng/ml, the circulating PRA levels are higher, which increases A-II, increases BP and blunts plasma renal blood flow (74h). The lower the level of Vitamin D₃, the greater the risk of incident hypertension, with the lowest quartile of serum Vitamin D₃ having a 52% incidence of hypertension versus the highest quartile having a 20% incidence [141]. Vitamin D₃ markedly suppresses renin transcription by a vitamin D receptor-mediated mechanism via the juxtaglomerular apparatus [133]. The role of vitamin D₃ in electrolyte levels, intravascular volume and BP homeostasis indicates that it is important in amelioration of

hypertension [133]. Vitamin D lowers ADMA, suppresses proinflammatory cytokines such as TNF- α , increases NO, improves endothelial function and arterial elasticity, decreases vascular smooth muscle hypertrophy, regulates electrolytes and blood volume, increases insulin sensitivity, reduces free fatty acid concentration, regulates the expression of the natriuretic peptide receptor and lowers HS-CRP [134–141].

The range in BP reduction with Vitamin D3 supplementation is 3.6/3.1–13.1/7.2 mmHg. The reduction in BP is related to the pretreatment level of Vitamin D3, the dose of vitamin D3 and serum level of vitamin D3, but BP is only reduced in hypertensive patients [141]. A vitamin D level of 60 ng/ml is recommended with the use of supplements or sunshine, as food intake will not usually achieve this blood level.

Vitamin B6

Low serum vitamin B6 (pyridoxine) levels are associated with hypertension in humans [143]. Subjects received 5 mg/kg/day of vitamin B6 for 4 weeks reduced BP by 8.4% 15/10 mmHg [144]. Vitamin B6 is a cofactor in neurotransmitter and hormone synthesis in the CNS, increases cysteine synthesis to neutralize aldehydes, enhances the production of glutathione, blocks calcium channels, improves insulin resistance, decreases central sympathetic tone and reduces end organ responsiveness to glucocorticoids and mineralocorticoids [1,37,38,145,146]. Vitamin B6 thus has a similar action to central α -agonists, diuretics and CCBs. The recommended dose is 200 mg per day orally by supplementation.

Flavonoids

The over 4000 flavonoids in fruits, vegetables, red wine, tea, soy and licorice may lower BP, CVA and CHD [147,148].

Resveratrol decreases augmentation index, improves arterial compliance and lowers central arterial pressure [149]. The central arterial pressure was reduced by dealcoholized red wine at 7.4 mmHg, and at 5.4 mmHg by regular red wine. Resveratrol increases flow-mediated vasodilation in a dose-related manner, improves endothelial dysfunction, prevents uncoupling of eNOS, increases adiponectin, lowers HS-CRP and blocks the effects of A-II [150–153]. The recommended dose is transresveratrol 250 mg per day from a certified supplement of high quality. It is not possible to get this dose from food [151].

Lycopene

Lycopene (carotenoid) lowers BP by 9/7 mmHg [154–158]. Patients treated with ACEI, CCBs and diuretics had a BP reduction of 5.4/3 mmHg in 6 weeks when given a standardized tomato extract [156]. Other studies have not shown changes in BP with lycopene [157]. The recommended daily intake of lycopene is 10–20 mg in food or supplement form.

Co-enzyme Q-10

Co-enzyme Q-10 (Co-Q-10; ubiquinone) is a potent lipid phase antioxidant, free radical scavenger, reduces oxidative stress, regenerates other vitamins and antioxidants, reduces oxidation of LDL, and is a cofactor and coenzyme in mitochondrial oxidative phosphorylation that lowers BP [1,159–161].

Serum levels of Co-Q-10 are lower in patients with hypertension [1,37,38]. Enzymatic assays showed a deficiency of Co-Q-10 in 39% of 59 patients with essential hypertension versus only 6% deficiency in controls ($p < 0.01$) [1], oral administration of 100–225 mg a day of Co-Q-10 lowers BP 17/10 mmHg [1,37,38,159–162]. Burke *et al.*, in 12-week randomized, double blind placebo controlled trial of 83 subjects with isolated systolic hypertension, given 60 mg of Co-Q-10 orally demonstrated significant a reduction in SBP of 18 mmHg ($p < 0.01$) [161]. There was a 55% response rate with a greater than 4 mmHg reduction in SBP. In the responder group, the reduction in SBP was 26 mmHg. In a meta-analysis of 12 clinical trials with 362 patients comprising three randomized trials, one crossover study and eight open label studies the BP reduction ranged from 11 to 17 mmHg for SBP and 8.2–10 mmHg for DBP [162]. Co-Q-10 emulsification and nanoparticles improve intestinal absorption and serum levels [163].

A summary of the available data regarding Co-Q-10 is as follows [1,37,38,159–164]:

- Hypertensive patients have a sixfold greater incidence of serum deficiency;
- The therapeutic level is 3 μ g/ml and requires an oral intake of approximately 3–5 mg/kg/day of Co-Q-10;
- Patients with the lowest Co-Q-10 serum levels have the best BP response of 15/10 mmHg;
- BP reduction peaks at 4 weeks, but if the Co-Q-10 is stopped then the the BP will

return to its baseline levels within 2 weeks after discontinuation of Co-Q-10;

- Approximately 50% of patients can eliminate BP agents.

Co-Q-10 is highly recommended for the treatment of hypertension in a well-absorbed supplement form.

ALA

ALA is a thiol compound antioxidant that is both water and lipid soluble, which recirculates other vitamins and antioxidants such as vitamins C and E, and glutathione and cysteine [1,37,38,117,164,165]. ALA also binds endogenous aldehydes and provides sulfhydryl groups that help to close vascular calcium channels, lower SVR and BP [1,37,38,117], increases NO levels and stability, improves endothelial function, increases cyclic AMP, protects against peroxynitrite-induced damage, is a potent scavenger of ROS and RNS, chelates heavy and transition metals, downregulates CD4 expression on mononuclear cells, regulates immune function, reduces oxidative stress, inflammation and cell adhesion molecules through effects on NF- κ B and increases glutathione levels [1,37,38,117,164,165]. Most studies are in the spontaneously hypertensive rat model regarding the effects of ALA on the vasculature and BP, but several recent human studies have been conducted [164,166,167].

A combination of ALA (200 mg twice daily) and acetyl-L-carnitine (500 mg twice daily) increased the brachial artery diameter and BP was significantly decreased in the subgroup with metabolic syndrome (139 ± 21 – 130 ± 18 mmHg [$p = 0.03$ for SBP and $p < 0.06$ for DBP]) [164].

In the QUALITY study, 40 subjects with DM and stage I hypertension were randomized to quinapril 40 mg per day for 8 weeks or quinapril 40 mg per day with lipoic acid 600 mg per day [166]. Urinary albumin excretion decreased by 30% with quinapril alone and 53% with the combination of quinapril and lipoic acid ($p < 0.005$). The flow-mediated vasodilation increased 58% with quinapril alone and 116% the quinapril and lipoic acid combination ($p < 0.005$). BP was significantly reduced in both groups by 10%. However, another study showed no change in supine BP or pulse wave velocity with 1200 mg of ALA for 8 weeks [167]. Morcos *et al.*, showed stabilization of urinary albumin excretion in DM subjects given 600 mg

of ALA compared with placebo for 18 months ($p < 0.05$) [168].

Lipoic acid also has effects on established atherosclerosis in some animal models [169]. Over a period of 12 weeks, rabbits had a reduction in body weight, reduced aortic plaque, improved vascular reactivity, decreased NF- κ B, decreased oxidative stress, reduced cell adhesion molecule expression and selectins, and decreased T-cell content in plaque and reduced T-cell migration and adhesion.

The recommended dose is 100–200 mg per day of (*R*)-lipoic acid with biotin 2–4 mg per day to prevent biotin depletion with long term use of lipoic acid. (*R*)-lipoic acid is preferred to the L-isomer because of its preferred use by the mitochondria [1,37,38].

L-arginine

L-arginine and endogenous methylarginines are precursors for NO, mediated through conversion of L-arginine to NO by eNOS. L-arginine improves ED, reduces vascular tone, improves coronary artery blood flow, decreases angina, reduces symptoms of peripheral artery disease and lowers BP [1,37,38,170–172]. The circulating arginine in plasma in both healthy patients and those with vascular disease is 30-fold higher than the Michaelis–Menton constant values for eNOS [172]. However, molecular uncoupling of eNOS may occur in the absence of tetrahydrobiopterin, which stabilizes eNOS. This uncoupling leads to production of ROS and may increase BP [172]. Administration of tetrahydrobiopterin improves BP, cardiac function and left ventricular hypertrophy [172]. Patients with hypertension, hyperlipidemia, DM and atherosclerosis have increased levels of HSCRP and inflammation, increased microalbumin, low levels of apelin (stimulates NO in the endothelium), increased levels of arginase (breaks down arginine) and elevated serum levels of ADMA, which inactivates NO [171,173–176].

As mentioned above, under normal physiological conditions, intracellular arginine levels far exceed the K_m of eNOS. However, endogenous NO formation is dependent on extracellular arginine concentration. The NO production in endothelial cells is closely coupled to cellular arginine update, indicating that arginine transport mechanisms play a major role in the regulation of NO-dependent function. Exogenous arginine can increase renal vascular

and tubular NO bioavailability and influence renal perfusion, function and BP. Numerous studies demonstrate an antihypertensive effect of arginine that is similar to that in the DASH I diet [170,171,177–180]. BP decreased by 6.2/6.8 mmHg with 10 g per day of L-arginine when provided as a supplement or through natural foods to a group of hypertensive subjects [170]. Arginine given at 4 g per day also significantly lowered BP in women with gestational hypertension without proteinuria, reduced the need for antihypertensive therapy, decreased maternal and neonatal complications and prolonged the pregnancy [177,178]. The combination of arginine (1200 mg per day) and N-acetyl cysteine (600 mg twice per day) administered over 6 months to hypertensive patients with Type 2 diabetes, lowered SBP and DBP ($p < 0.05$), increased HDL-C, decreased LDL-C and oxLDL, reduced HSCRP, ICAM, VCAM, PAI-I, fibrinogen and IMT [179]. A study of 54 hypertensive subjects given arginine 4 g three-times per day for 4 weeks had significant reductions in 24 h ABM [180]. Arginine is recommended for the treatment of hypertension.

L-carnitine

Carnitine may be useful in the treatment of essential hypertension, Type 2 DM with hypertension, hyperlipidemia, cardiac arrhythmias, CHF and cardiac ischemic syndromes [1,181–183]. Doses of 2–3 g twice per day are recommended.

Taurine

Patients with essential hypertension have reduced urinary taurine [1,184,185]. Taurine lowers BP, SVR and heart rate, decreases sympathetic nervous system activity and urinary sodium and water excretion, increases atrial natriuretic factor, improves insulin resistance, increases NO and improves endothelial function, decreases A-II, PRA, aldosterone, plasma norepinephrine, plasma and urinary epinephrine [1,184–186]. A study of Japanese males showed a BP reduction of 14.8/6.6 mmHg [187]. Fujita *et al.* demonstrated a reduction in BP of 9/4.1 mmHg in hypertension subjects given 6 g of taurine for 7 days [185]. The recommended dose of taurine is 2–3 g per day [1,37,38,184–188].

Pycnogenol

Pycnogenol, reduced systolic BP from 139.9–132.7 mmHg ($p < 0.05$) in 11 patients

with mild hypertension in 2 months. Diastolic BP fell from 93.8 to 92.0 mmHg (not significant). Pycnogenol is a pine bark derivative that acts as a natural ACEI, protects cell membranes from oxidative stress, increases NO and improves endothelial function, reduces serum thromboxane concentrations, decreases myeloperoxidase activity, improves renal cortical blood flow, reduces urinary albumin excretion and decreases HS-CRP [189–193]. Other studies have shown reductions in BP and a decreased need for ACEIs and CCBs, reductions in ET-1, HgA1C, fasting glucose and LDL-cholesterol [190,191,193]. It is highly recommended in supplement form.

Dark chocolate & cocoa

Dark chocolate (100 g) and cocoa with a high content of polyphenols (≥ 30 mg) has been shown to significantly reduce BP in humans [194–203]. A meta-analysis of 173 hypertensive subjects given cocoa for a mean duration of 2 weeks had a significant reduction in BP of 4.7/2.8 mmHg ($p = 0.002$ for SBP and 0.006 for DBP) [194]. Fifteen subjects given 100 g of dark chocolate with 500 mg of poly-phenols for 15 days had a 6.4 mmHg reduction in SBP ($p < 0.05$) with a nonsignificant change in DBP [195]. Cocoa at 30 mg of polyphenols reduced BP in prehypertensive and stage I hypertensive patients by 2.9/1.9 mmHg at 18 weeks ($p < 0.001$) [196]. Two more recent meta-analyses of 13 trials and ten trials with 297 patients found a significant reduction in BP of 3.2/2.0 mmHg and 4.5/3.2 mmHg, respectively [198,201]. The BP reduction is greatest in those with the highest baseline BP and those with at least 50–70% cocoa at doses of 6–100 g per day [198,200]. Cocoa may also improve insulin resistance and endothelial function [195,202,203].

Sesame

Sesame has been shown to reduce BP in a several small randomized, placebo-controlled human studies over 30–60 days [204–209]. Sesame lowers BP alone [205–209] or in combination with nifedipine [204,208] and with diuretics and β -blockers [205,209]. In a group of 13 mild hypertensive subjects, 60 mg of sesamin for 4 weeks lowered SBP 3.5 mmHg ($p < 0.044$) and DBP 1.9 mmHg ($p < 0.045$) [206]. A black sesame meal at 2.52 g per day over 4 weeks in 15 subjects reduced SBP by 8.3 mmHg ($p < 0.05$) but there was a nonsignificant reduction in

DBP of 4.2 mmHg [207]. In addition, sesame lowers serum glucose, HgBAIC and LDL-C, increases HDL, reduces oxidative stress markers and increases glutathione, SOD, GPx, CAT, vitamins C, E and A [204,205,207–209]. The active ingredients are natural ACEIs, sesamin, sesamol, sesaminol glucosides, furoufuran lignans and suppressors of NF-κB [210,211]. All of these effects lower inflammation and oxidative stress, improve oxidative defense and reduce BP [210,211]. Sesame is recommended as a food or as a supplement in the forms reviewed.

Melatonin

Melatonin demonstrates significant anti-hypertensive effects in humans in numerous double-blind randomized placebo controlled clinical trials [212–222]. Melatonin at 2.5 mg at night for 3 weeks, in a group of 16 hypertensive men, lowered nocturnal BP by 6/4 mmHg and reduced the day/night amplitudes of SBP by 15% and DBP by 25%, improved nocturnal dipping, improved sleep and reduced cortisol levels with no change in heart rate [212]. Melatonin at 5 and 10 mg per night significantly amplified the nocturnal decline in DBP and SBP compared with placebo in hypertensive diabetic subjects [213,214] and significantly decreased nocturnal BP in women on 3 mg per night without influence on diurnal BP [215]. In 38 treated hypertensive patients on a stable drug regimen, with confirmed nocturnal hypertension, melatonin time-released preparation at 2 mg at night significantly reduced BP by 6/3 mmHg [216]. However, it is important to monitor 24 h ABM in such patients to determine if melatonin results in an improved dipping status or may actually result in extreme dipping or reverse dipping [217,219]. Several studies indicate that in hypertensive patients with CHD, only 30.8% had improvement in circadian patterns, approximately 46.2% remained nondippers, 15.4% became extreme dippers and 7.6% became reverse dippers [217,221]. Melatonin may improve BP responses when added to an Angiotensin receptor blocker (ARB) [220]. Melatonin at a dose of 5 mg/day for 2 months in 30 subjects with metabolic syndrome, significantly improved BP, LDL-C and oxidative stress markers such as TBARS and catalase [222]. Hypertensive patients have altered circadian pacemaker function, disturbed autonomic cardiovascular regulation with blunted day to night sympathetic and parasympathetic tone,

reduced vasodilation and suppressed nocturnal melatonin levels, especially in nondippers, by up to 50% as measured by urinary melatonin and metabolites (6-hydroxymelatonin sulfate), and salivary melatonin [223–229]. Low urinary melatonin is an independent risk factor for incident hypertension [229]. Melatonin has actions in all organs, especially the heart and arteries. Melatonin lowers serum myeloperoxidase which contributes to its antihypertensive and antioxidant effects [230]. Its mechanism of action is via the G-protein-coupled receptor on Mel1A and Mel1B receptors in vascular tissues, binds with calmodulin in both cytosolic and nuclear binding sites via three different receptors and through the suprachiasmatic autonomic nucleus that regulates 24 h biological rhythms by endocrine and autonomic mechanisms, as well as pineal melatonin secretion [212,231]. In addition, the antihypertensive effect is mediated by GABA_A receptors and inhibition of plasma

Table 2. Lifestyle recommendations for hypertension.

Factor	Measure
<ul style="list-style-type: none"> ■ Exercise: <ul style="list-style-type: none"> ▪ Aerobically 20 min daily; 4200 kJ/week ▪ Resistance training at 40 min per day 	<ul style="list-style-type: none"> 7 days/weeks 7 days/week
<ul style="list-style-type: none"> ■ Weight loss: <ul style="list-style-type: none"> ▪ To IBW ▪ Lose 1–2 lb/week ▪ BMI <25 ▪ Waist circumference <ul style="list-style-type: none"> – <35 inches in female – <40 inches in male ▪ Total body fat <ul style="list-style-type: none"> – <16% in males – <22% in females ▪ Increase lean muscle mass 	–
<ul style="list-style-type: none"> ■ Alcohol restriction: <ul style="list-style-type: none"> ▪ Wine <10 oz (preferred – red wine) ▪ Beer <24 oz ▪ Liquor <2 oz (100 proof whiskey) 	<20 g/day
<ul style="list-style-type: none"> ■ Caffeine restriction or eliminate depending on CYP 450 type 	<100 mg/day
<ul style="list-style-type: none"> ■ Tobacco and smoking 	Stop
<ul style="list-style-type: none"> ■ Avoid drugs and interactions that increase BP 	–

BP: Blood pressure; IBW: Ideal body weight.

Table 3. Vitamins, antioxidants and nutraceutical supplements.

Nutrient	Daily intake
Vitamin C	250–500 mg b.i.d.
Vitamin E (mixed tocopherol/tocotrienols)	400 IU q.i.d.
Vitamin B6	100 mg q.i.d.to b.i.d.
Coenzyme Q-10	100 mg q.i.d. to b.i.d.
Lipoic acid (with biotin)	100–200 mg b.i.d.
L-carnitine	1000–2000 mg b.i.d.
Taurine	1.0–3.0 g b.i.d.
L-arginine (food and supplements)	5 g b.i.d.
Trans resveratrol	250 mg q.i.d.
Vitamin D3	To serum level of 60 ng/ml
Melatonin	2.5 mg
Chlorogenic acids	150–200 mg
Pomegranate juice	8 oz
Grape seed extract	300 mg

b.i.d.: Twice a day; q.i.d.: Four-times a day.

A-II levels [231]. All of these mechanisms induce vasodilation, improve endothelial dysfunction and NO bioavailability and provide antioxidant activity and antiremodeling action [225,232,233]. β -blockers reduce melatonin secretion [234].

Chlorogenic acids & green coffee bean extract

Polyphenols, chlorogenic acids (CGAs), the ferulic acid metabolite of CGAs and di-hydro-caffeic acids decrease BP in a dose-dependent manner, increase eNOS and improve endothelial function in humans [235–240]. CGAs in green coffee bean extract at doses of 140 mg per day significantly reduced SBP and DBP in 28 subjects in a placebo-controlled randomized clinical trial [235]. A study of 122 male subjects demonstrated

a dose response in SBP and DBP with doses of CGA from 46 mg to 185 mg per day. The group that received the 185 mg dose had a significant reduction in BP of 5.6/3.9 mmHg ($p < 0.01$) over 28 days [240]. Another component of coffee beans, hydroxyhydroquinone, reduces the efficacy of CGAs in a dose-dependent manner, which partially explains the conflicting results of coffee ingestion on BP [237,239]. In addition, the *CYP1A2* genotype (the main enzyme responsible for the metabolism of caffeine) modifies the association between coffee intake, amount of coffee ingested and the risk of hypertension, heart rate, MI, arterial stiffness, arterial wave reflections and urinary catecholamine levels [241–243]. The slow metabolizers (IF/IA allele), which is carried by 59% of the population, had a 3.00 hazard ratio for incident hypertension in the heavy coffee drinkers, whereas the fast metabolizers (IA/IA allele) had a 0.36 hazard ratio for incident hypertension [241].

Miscellaneous other compounds

Various other nutraceutical compounds have preliminary evidence of modest reductions in BP in humans including hesperidin, pomegranate juice, grape seed extract and hawthorne [244–252]. Hesperidin significantly lowered DBP 3–4 mmHg ($p < 0.02$) and improved microvascular endothelial reactivity in 24 obese hypertensive male subjects in a randomized, controlled crossover study over 4 weeks for each of three treatment groups, consuming 500 ml of orange juice, hesperidin or placebo [244]. Pomegranate juice reduces SBP by 5–12%, reduces serum ACE activity by 36%, and has antiatherogenic, antioxidant and anti-inflammatory effects [245–248]. Pomegranate juice at 50 ml per day reduced carotid IMT by 30% over 1 year, increased paraxonase by 83%, decreased oxLDL by 59–90%, decreased antibodies to oxLDL by 19%, increased total antioxidant status by 130%, reduced TGF- β , increased catalase, superoxide dismutase and GPx [246]. Grape seed extract (GSE) was administered to subjects in nine randomized trials, meta-analysis of 390 subjects and demonstrated a significant reduction in SBP of 1.54 mmHg ($p < 0.02$) [249]. Significant reduction in BP of 11/8 mmHg ($p < 0.05$) was seen in another dose–response study with 150–300 mg per day of GSE over 4 weeks [250]. GSE has high phenolic content which activates the PI3K–Akt

Box 1. Combination therapies.

- Sesame with β -blockers, diuretics and nifedipine
- Pycnogenol with ACEI
- Lycopene with various antihypertensive medications
- (R)-Lipoic acid with ACEI
- Vitamin C with CCBs
- N-acetyl cysteine with arginine
- Garlic with ACEI, diuretics and β -blockers
- Co-enzyme Q-10 with ACEIs and CCBs

ACEI: Angiotensin converting enzyme inhibitor; CCB: Calcium channel blocker.

signaling pathway that phosphorylates eNOS and increases NO [250,251]. Hawthorne extract demonstrated borderline reductions on BP in patients not taking antihypertensive agents at 500 mg per day ($p < 0.081$) and significantly reduced DBP ($p < 0.035$) in diabetic patients taking antihypertensive drugs at doses of 1200 mg per day of hawthorn extract [252,253]. More controlled studies in humans are needed to confirm these initial findings with all of the compounds (Tables 2 & 3).

Combination therapy

This article has reviewed numerous combinations of nutraceutical supplements with antihypertensive drugs that have been shown to have additional BP lowering effects (Box 1).

Nutrient–antihypertensive drug interactions

Many antihypertensive drugs may cause nutrient depletions that can actually interfere with their antihypertensive action or cause other metabolic adverse effects to manifest through the laboratory or with clinical symptoms [254–256]. Diuretics decrease potassium, magnesium, phosphorus, sodium, chloride, folate, vitamin B6, zinc, iodine and Co-Q-10, increase homocysteine, calcium and creatinine and elevate serum glucose by inducing insulin resistance. β -blockers reduce Co-Q-10 and ACEI and ARBs reduce zinc.

Natural antihypertensive compounds categorized by antihypertensive class

Nutraceutical supplements and food may have similar actions to certain antihypertensive drugs. Box 2 categorizes these natural compounds into the major antihypertensive drug classes

Therapeutic approach

A very effective approach for selecting nutritional supplements in patients on antihypertensive agents in order to reduce pharmacologic therapy involves the measurement of intracellular micronutrients in lymphocytes, plasma renin activity and serum aldosterone followed by repletion of all micronutrient depletions with selected higher doses of nutritional supplements [256]. The combination of the DASH 2 diet, weight management, exercise and nutrient supplementation resulted in a complete repletion of nutrients and antioxidant levels in 6–12 months

Box 2. Natural antihypertensive compounds categorized by antihypertensive class.

- Diuretics
 - Hawthorne Berry
 - Vitamin B6 (Pyridoxine)
 - Taurine
 - Celery
 - GLA
 - Vitamin C (Ascorbic Acid)
 - K⁺
 - Mg⁺⁺
 - Ca⁺⁺
 - Protein
 - Fiber
 - Coenzyme Q-10
 - L-carnitine
- BBs
 - Hawthorne Berry
- CCAs (reduce SNS activity)
 - Taurine
 - K⁺
 - Zinc
 - Na⁺ Restriction
 - Protein
 - Fiber
 - Vitamin C
 - Vitamin B6
 - Coenzyme Q-10
 - Celery
 - GLA/DGLA
 - Garlic
- Direct Vasodilators
 - ω -3 FA
 - MUFA (ω -9 FA)
 - K⁺
 - Mg⁺⁺
 - Ca⁺⁺
 - Soy
 - Fiber
 - Garlic
 - Flavonoids
 - Vitamin C
 - Vitamin E
 - Coenzyme Q-10
 - L-Arginine
 - Taurine
 - Celery
 - ALA

ACEI: Angiotensin converting enzyme inhibitor; ALA: α -lipoic acid; ARB: Angiotensin receptor blocker; BB: β -blocker; CCA: Central α -agonist; CCB: Calcium channel blockers; DGLA: dihomo- γ -linolenic acid; DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; FA: Fatty acid; GLA: γ -linolenic acid; MUFA: Monounsaturated fatty acid; NAC: N-acetyl cysteine; SNS: Sympathetic nervous system.

Box 2. Natural antihypertensive compounds categorized by antihypertensive class (cont.).

- CCBs
 - ALA
 - Vitamin C (Ascorbic Acid)
 - Vitamin B6 (Pyridoxine)
 - Magnesium (Mg²⁺)NAC
 - Vitamin E
 - Hawthorne Berry
 - Celery
 - ω-3 Fatty Acids (EPA and DHA)
 - Calcium
 - Garlic
- ACEIs
 - Garlic
 - Seaweed – various (e.g., Wakame)
 - Tuna protein/muscle
 - Sardine protein/muscle
 - Hawthorne berry
 - Bonito fish (dried)
 - Pycnogenol
 - Casein
 - Hydrolyzed whey protein
 - Sour Milk
 - Geletin
 - Sake
 - Essential fatty acids (ω-3 FA)
 - Chicken egg yolks
 - Zein
 - Dried salted fish
 - Fish sauce
 - Zinc
 - Hydrolyzed wheat germ isolate
- ARBs
 - Potassium (K⁺)
 - Fiber
 - Garlic
 - Vitamin C
 - Vitamin B6 (Pyridoxine)
 - Coenzyme Q-10
 - Celery
 - GLA and DGLA
 - Resveratrol

ACEI: Angiotensin converting enzyme inhibitor; ALA: α-lipoic acid; ARB: Angiotensin receptor blocker; BB: β-blocker; CCA: Central α-agonist; CCB: Calcium channel blockers; DGLA: dihomo-γ-linolenic acid; DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; FA: Fatty acid; GLA: γ-linolenic acid; MUFA: Monounsaturated fatty acid; NAC: N-acetyl cysteine; SNS: Sympathetic nervous system.

with 62% of patients being able to discontinue all antihypertensive drugs and maintain a normal BP of 120/80–126/84 mmHg. The implications

of this approach are enormous in both savings in drug costs and adverse effects to the patients. For BP drugs alone the savings in the USA could be over US\$12 billion [256].

Summary

Hypertension is a disease characterized by inflammation, oxidative stress and immune dysfunction in the vascular system. The increase in BP is a bidirectional issue with vascular endothelial dysfunction leading to hypertension and the hypertension increasing the endothelial dysfunction. A more logical approach to the prevention and treatment of hypertension is to address the underlying pathophysiology, as noted above, to improve vascular function and lower BP. This approach will improve cardiovascular outcomes. The scientific literature supports the use of nutrition and nutraceutical supplements for the effective management of hypertension that is safe and void of most adverse effects. In addition, this approach offers potential cost savings to patients and reduces the need for drugs.

Future perspective

As we gain more knowledge regarding the mechanisms of action, doses and optimal combinations of nutraceutical supplements for the prevention and treatment of hypertension, their clinical use will expand. Their use will also enhance the effects of other nondrug treatments and provide additive or synergistic effects to drug therapy. The most logical way to treat hypertension is to address the blood vessel pathology and correct endothelial dysfunction, increase NO and correct inflammation, oxidative stress and immune dysfunction of the arteries. Stratification of patients based on nutrigenomics and metabolomics will improve the selection of nutritional supplements to manage hypertension.

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