

Combination Nutraceutical Supplement Lowers Blood Pressure in Hypertensive Individuals

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Abstract

Context: Blood pressure (BP) increases with age as a consequence of the interaction of genetics, the environment, and the dietary intake of both macronutrients and micronutrients. Essential nutritional deficiencies are very common and may be even more common in individuals with hypertension. In recent years, numerous clinical trials using nutraceuticals and functional foods have attracted interest as potential therapies for the treatment of hypertension.

Objective: The research team intended to evaluate the benefits of a blend of seven nutrients (actives) in lowering BP in individuals with hypertension.

Design: This study was a randomized, double-blind, placebo-controlled clinical trial using human participants. All participants who had been taking BP medications discontinued their use for a period of 1 mo prior to entering the study.

Setting: The study occurred at the Hypertension Institute in Nashville, TN, USA.

Participants: At the start of the study, the intervention group included 22 participants, and the control group included 20. Dr Houston recruited participants from his patients with hypertension, (systolic blood pressure [SBP] ≥ 140 mm Hg and/or diastolic blood pressure [DBP] ≥ 90 mm Hg).

Intervention: The intervention, the active blend, was a dietary supplement in powder form that was given in a daily serving and included (1) vitamin C (as magnesium ascorbate), 1000 mg; (2) grape seed extract, 150 mg; (3)

magnesium (from ascorbate), 87 mg; (4) vitamin B₆ (as pyridoxine HCl), 100 mg; (5) vitamin D₃, 2000 IU; (6) biotin, 2 mg; and (7) taurine, 6 g. The placebo consisted of an identically labeled bottle containing only rice syrup solids.

Outcome Measures: The research team measured BP at baseline and at wk 2, 4, and 6. With participants in a sitting position, the research team measured their BPs three times at 2-min intervals using the left arm and following the American Heart Association's guidelines for BP measurement using a mercury sphygmomanometer.

Results: The active group's BP was lowered from an initial SBP value of 144.01 mm Hg to 130.77 mm Hg at wk 2 ($P < .300$) and to 128.05 mm Hg ($P < .001$) at wk 4. That group also lowered its DBP from an initial 91.86 mm Hg to 81.83 mm Hg ($P < .100$) at wk 2 and 80.51 mm Hg ($P < .083$) at wk 4. Because of the loss of participants in the intervention group, the research team limited the reporting of the study's results to the data obtained after 4 wk. As compared to the placebo at wk 4, the active group had a greater decrease in both SBP ($P = .001$) and DBP ($P = .083$). No adverse effects were noted in the study.

Conclusion: Intake of essential nutrients or dietary factors, such as taurine and/or grape seed extracts, can aid in the regulation of BP in individuals with hypertension.

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Hypertension is diagnosed when systolic blood pressure (SBP) is ≥ 140 mm HG and/or diastolic blood pressure (DBP) is ≥ 90 mm Hg. Approximately 50 to 60 million people in the United States have hypertension, and according to the National Health and Nutritional Examination Survey (NHANES III), only 27% of this population controls the disease. Blood pressure (BP) increases with age, and about two-thirds of people over 65 have hypertension. Starting at 115/75 mm Hg, cardiovascular risk doubles with each increment of 20/10 mm Hg throughout the BP range.¹

Hypertension is a consequence of the interaction of environment and genetics. Macro- and micronutrients are crucial to the regulation of BP and the prevention of organ damage and atherosclerosis. Nutrient-gene interactions and oxidative stress, with the subsequent gene expressions, have either positive or negative influence on vascular biology in humans. Endothelial dysfunction (ED) and dysfunction of the vascular smooth muscle are the initiating and perpetuating factors in essential hypertension.²

Nitric oxide (NO) is a central regulator of vascular tone and homeostasis.³ Most NO in the vascular wall is produced by the endothelial cells via an enzyme, the endothelial nitric oxide synthase (eNOS). Oxidative stress may contribute to the pathogenesis of elevated BP. Free radicals such as superoxide can react with NO, forming peroxynitrite (ONOO⁻) and thereby lowering levels of NO in the endothelium. Lower levels of NO impair the endothelium-dependent vasorelaxation caused by the loss of NO bioavailability.⁴

Tetrahydrobiopterin (BH₄) is a cofactor for the production of NO by eNOS. BH₄ must be in a reduced state to act as a cofactor of eNOS. Vitamin C is a reducing agent that can maintain BH₄ in a reduced state.⁵

Macronutrient and micronutrient deficiencies are very common in the general population and maybe even more common in patients with hypertension. Replacement of individual micronutrient deficiencies, as well as high dose therapy of selected nutraceuticals has been shown to be beneficial in the treatment of hypertension. The objective of this study was to measure the BP response to combination nutraceutical supplement without changing the patients' normal daily habits.

Methods

Participants

This study was a randomized, double-blind, placebo-controlled clinical trial using human participants. The Hypertension Institute approved the study. The study involved no referrals by a primary care physician (PCP) because Dr Houston recruited 42 participants from his adult patients with hypertension—SBP \geq 140 mm Hg and/or DBP \geq 90 mm Hg. Dr Houston had confirmed their hypertension on three separate occasions as required by the American Heart Association's (AHA) criteria.

The inclusion criteria included SBP \geq 120 mm Hg or DBP \geq 90 mm Hg. Participants in the study were patients of the clinic. To participate in the study, the patients provided informed consent to the nurse. The patients were given sequential numbers. The odd-numbered patients received the active product and the even-numbered subjects received the placebo product. The study population comprised (1) 19 males with an average weight of 90.7 kg and an average resting heart rate of 70 beats per minute and (2) 23 females with an average weight of 65.3 kg and an average resting heart rate of 73 beats per minute. The exclusion criteria included (1) a myocardial infarction

within the prior 5 years; (2) clinical angina; (3) a history of cerebrovascular accident; (4) creatinine levels over 2.5 mg; (5) liver disease with AST, ALT, or alkaline phosphatase over $1.5 \times$ normal; (6) a known cancer within the prior 5 years; (7) congestive heart failure; and (8) a known allergy or sensitivity to any of the components of the treatment given to the intervention and control groups.

Participants were asked to maintain their normal daily habits: weight, exercise regimen, intake of diet/nutritional supplements, alcohol intake, tobacco use, and caffeine intake. All participants who had been taking BP medications discontinued their use for a period of 1 month prior to entering the study.

Intervention

Twenty-two participants received the intervention, the active blend, and 20 received the placebo. The active blend was a dietary supplement in powder form, given in a daily serving that included (1) vitamin C (as magnesium ascorbate), 1000 mg; (2) grape seed extract, 150 mg; (3) magnesium (from ascorbate), 87 mg; (4) vitamin B₆ (as pyridoxine HCl), 100 mg; (5) vitamin D₃, 2000 IU; (6) biotin, 2 mg; and (7) taurine, 6 g. The placebo consisted of an identically labeled bottle containing only rice syrup solids. The lot numbers were different for the active and placebo products.

The dose of the nutrients used in the study was based upon (1) normal daily dietary deficiencies, or (2) their reported beneficial effects in previous studies. Both magnesium as 100 mg per day and vitamin D as 2000 IU per day were chosen based upon normal clinical doses used in the clinic. The dose of biotin, vitamin B₆, vitamin C, and grape seed extract was based upon findings reporting increased endothelial nitric oxide production in hypertensive studies. The dose of taurine was based upon a treatment study of patients with borderline hypertension.

Procedures

The patients selected for the study discontinued the use of BP products to control their hypertension for a period of 30 days prior to the study. At the end of that 30-day period, the patients returned to the clinic for a blood-pressure reading, heart rate, and weight measured by the clinic's nurse. The patients at that time, week 0 of the study, were given either a placebo or active product. Baseline readings began at week 0. Each patient was required to return every 2 weeks for additional readings. At each visit, BP, weight, and pulse rate were measured.

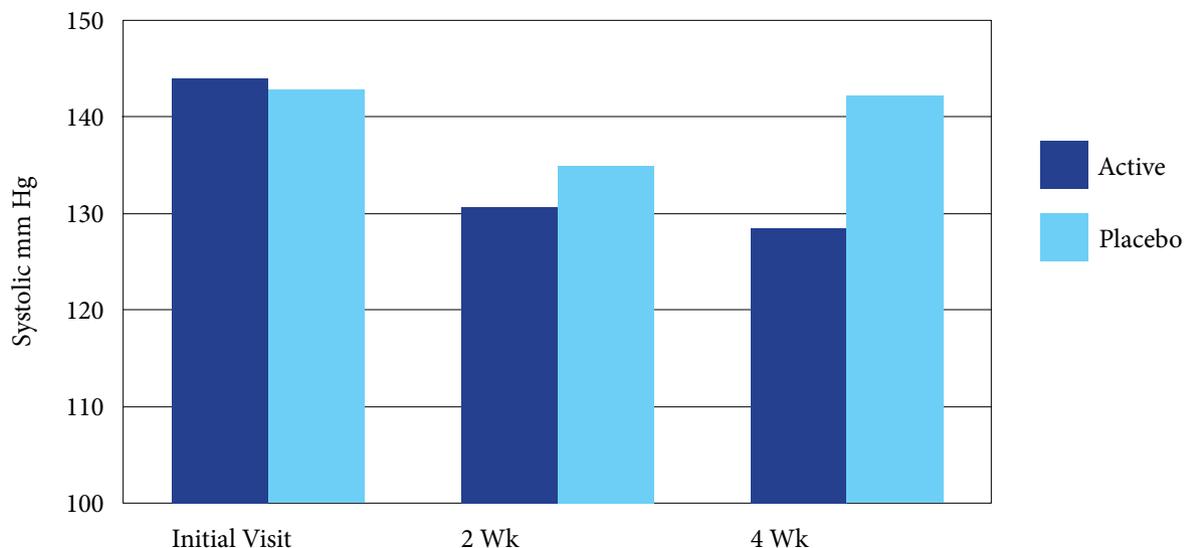
Outcome Measures

The research team measured BP at baseline and at weeks 2, 4, and 6. While participants were in a sitting position, the research team measured their BPs three times at 2-minute intervals using the left arm and following the American Heart Association's guidelines for BP measurement using a mercury sphygmomanometer.

Table 1. Systolic Blood Pressure

	Active Group Mean (SD)	Control Mean (SD)	Difference	P Value
Baseline	144.01 (12.57)	142.86 (12.86)	-1.15	.780
Week 2	130.77 (10.69)	134.90 (13.85)	4.13	.300
Week 4	128.05 (10.18)	142.16 (12.99)	14.11	.001

Figure 1. Systolic mm Hg for Active Product vs Placebo



The investigator and recorded any adverse effects of the treatment at each visit. Participants' BPs were not taken if they told the investigator that they were ill.

Results

Initially 22 participants were supplied with the active product. For the intervention group, the research team tested BP (1) for 22 participants at week 2, (2) for 17 at week 4, and (3) for only 7 at week 6. Participants gave a number of reasons for not attending the third visit, including deciding to drop out of the study and not feeling well. Because only seven of the original 22 active participants were tested at week 6, standard *t* testing to determine the *P* value for that time could not be conducted.

The control group began with 20 participants. For that group, the research team tested BP (1) for 17 participants at week 2, (2) for 17 at week 4, and (3) for 16 at week 6. No adverse effects were noted in the study.

Because of the loss of participants in the intervention group, the research team has limited the reporting of the study's results to the data obtained after 4 weeks. As compared to the placebo at week 4, the active group had a greater decrease of both SBP (*P* = .001) and DBP (*P* = .083)

Systolic Blood Pressure

The active group's SBP was lowered from an initial value of 144.01 mm Hg to 130.77 mm Hg at week 2 (*P* < .005) and to 128.05 mm Hg (*P* < .005) at week 4 (Table 1). The mean decrease for the active group from baseline to week 2 was 13.24 mm Hg and to week 4 was 15.9 mm Hg.

Figure 1 compares the observed mean SBP of the active to the control group at baseline, week 2, and week 4. The active group had a lower mean SBP than the controls at weeks 2 and 4. The mean decrease for the active as compared to the control group was 4.13 mm Hg at week 2 (*P* = .30) and 14.11 mm Hg at week 4 (*P* = .001).

Diastolic Blood Pressure

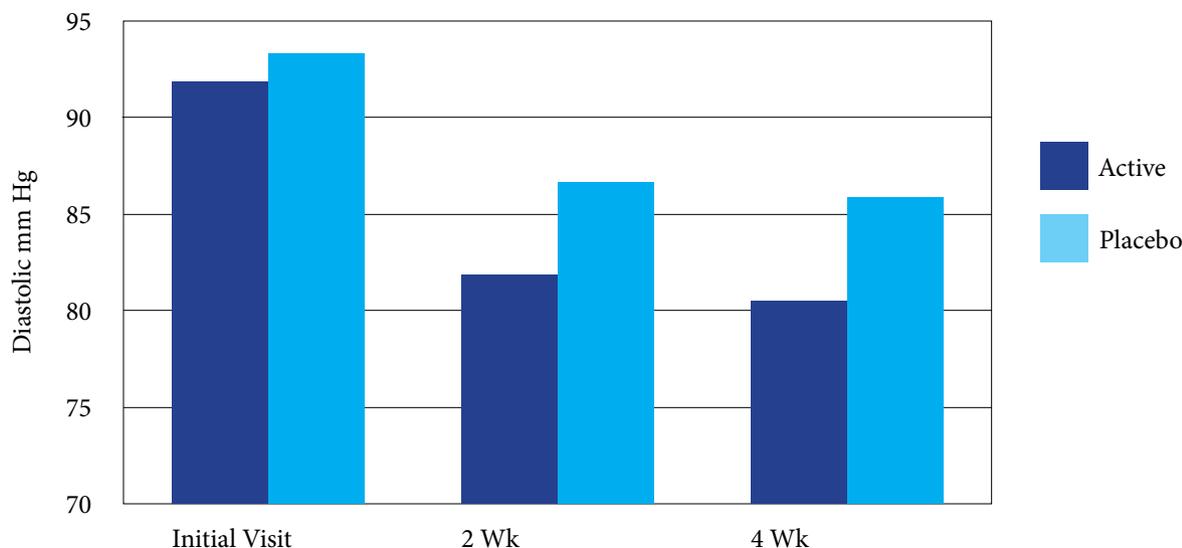
The active group lowered its DBP from an initial 91.86 mm Hg to 81.83 mm Hg (*P* < .017) at week 2 and to 80.51 mm Hg (*P* < .017) at week 4 (Table 2). The mean decrease in DBP for the active group from baseline to week 2 was 10.03 mm Hg and to week 4 was 11.35 mm Hg.

Figure 2 compares the observed mean DBP of the active group to that of the control group at baseline, week 2, and week 4. The active group's mean decrease was 4.99 mm Hg greater than the controls at week 2 (*P* = .10) and 5.36 mm Hg greater at week 4 (*P* = .083).

Table 2. Diastolic Blood Pressure

	Active Group Mean (SD)	Control Mean (SD)	Difference	P Value
Baseline	91.86 (3.69)	93.33 (3.11)	1.47	.608
Week 2	81.83 (7.19)	86.82 (10.57)	4.99	.100
Week 4	80.51 (8.99)	85.87 (8.27)	5.36	.083

Figure 2. Diastolic mm Hg for Active Product vs Placebo



Discussion
Vitamin C

Vitamin C levels in plasma are reported to be inversely related to BP as well as cardiovascular disease.^{6,7} In a cross-section analysis of 242 women done over a 10-year period, persons in the highest quartile of plasma-ascorbate levels had a 4.66 mm Hg lower systolic BP and a 6.04 mm Hg lower diastolic BP as compared to those individuals in the lowest quartile. Although evidence for the BP-lowering effect of vitamin C in clinical trials has been inconsistent, Juraschek et al found mean reductions of 4.85 mm Hg for SBP and 1.67 mm Hg for DBP in a meta-analysis of 29 trials of hypertensive individuals. The mean dose of vitamin C in the meta-analysis was 500 mg/day, and the mean duration of the studies was 8 weeks.⁸

In a randomized, double-blind, controlled trial, hypertensive participants were given 500, 1000, or 2000 mg of vitamin C for a period of 8 months. Vitamin C lowered SBP 4.5 mm HG and DBP 2.8 mm Hg. No additional BP benefit occurred for doses greater than 500 mg.⁹ Vitamin C has also been shown to aid in reducing BP in elderly individuals with refractory hypertension.¹⁰

As a scavenger of free radicals, the mechanism by which vitamin C lowers BP was suggested in 1997 as the scavenging of superoxide anions.¹¹ NO is produced from

L-arginine by the endothelial isoform of eNOS. NO that is released by the vascular endothelium cells is one of the principle mechanisms for vasodilation.¹² Superoxide anions react with NO to produce peroxynitrite (ONOO-), thereby lowering plasma levels of NO. ONOO- uncouples eNOS by the oxidation of the eNOS cofactor tetrahydrobiopterin (BH₄).¹³ Kinetic studies have shown that vitamin C cannot preserve NO bioactivity through superoxide scavenging, even at levels of vitamin C considered to be saturated in the plasma (100 μM).

Cellular BH₄ levels are dependent on the concentration of ascorbate. Only the completely reduced form of BH₄ supports NO synthesis by eNOS. Ascorbic acid is proposed to maintain BH₄ in a reduced state.¹⁴ In vitro studies with ascorbate show that 10 μM to 100 μM of ascorbate will stabilize the reduced form of BH₄ in endothelial cells. The phosphorylation of eNOS, which is known to increase eNOS activity, was increased in a dose-dependent manner by ascorbate.¹⁵ The increased phosphorylation of eNOS reached a significant value of *P* < .001 at 80 μM ascorbate.¹⁶

In a review of the daily need for vitamin C in healthy persons, Levine found that plasma and circulating cells saturated at 400 mg per day in healthy young women. This study documented an increased need for vitamin C in the

diet, which resulted in the Food and Nutrition Board raising the RDA for vitamin C.¹⁷

Grape Seed Extracts

Plant polyphenols occur in all plant foods and can be divided into 10 or more different subclasses according to their chemical structure. The consumption of red wine has been shown to be associated with a lower incidence of cardiovascular disease, such as hypertension.¹⁸ Grape seed extracts (GSE) contain polyphenolic compounds. GSE has been shown to activate the P13K/AKT signaling pathway through a redox-sensitive mechanism. Activation of the cellular signaling pathway results in the phosphorylation of eNOS and subsequent production of NO.¹⁹ Grape polyphenols have also been shown to prevent oxidative stress by inhibiting NADPH oxidase (NOX) activity. NOX produces the superoxide radical that may result in the lowering of NO.²⁰

Kappagoda et al reported the effects of a standardized GSE using 30 prehypertensive participants. At the end of 8 weeks, a dose of 300 mg GSE per day lowered SBP by 8 mm Hg ($P = .003$) and DBP by 5 mm Hg ($P < .05$). Smokers (abstinence for < 1 y) were excluded from this study as well as those having clinical evidence of coronary artery, pulmonary, gastrointestinal, or renal disease or those individuals consuming prescription medications or vitamin preparations.²¹

Ward et al reported the effects of another standardized GSE using 69 treated, hypertensive individuals with a mean SBP of ≥ 125 mm Hg. At the end of 6 weeks, the daily consumption of 1000 mg of GSE did not have any effect on BP. At the end of 6 weeks of daily consumption of 1000 mg of the same GSE and 500 mg vitamin C/day increased both SBP by 4.8 mm Hg ($P < .0001$) and DBP by 2.7 mm Hg ($P < .0001$). Ward's study reported a negative effect on BP at the end of 6 weeks.²²

Grape seeds contain 5% to 8% flavonoids by weight. The GSE used by Kappagoda was characterized by a high amount (25%-50%) of phenolic compounds with low molecular weights. The GSE used by Ward was characterized as $< 17\%$ phenolic compounds with low molecular weights. Ward's GSE contained 50.6% total phenolic compounds whereas the Kappagoda GSE contained a total of 80% total phenolic compounds.²³ Commercial sources of GSE vary with respect to total phenolic compounds and the percentage of phenolic compounds with low molecular weights as well as to standardized measures of in vitro antioxidant activities.²⁴ The GSE used in the current study contained a high amount of flavonoids with a low molecular weight and a high percentage of total phenolic compounds.

Magnesium

In a study of 615 men, Joffres reported that magnesium intake seemed to be the nutrient with the strongest inverse association with BP, out of a total of 61 dietary

variables.²⁵ Magnesium deficiency has been reported to promote atherosclerosis, thrombosis, and hypertension.²⁶ Magnesium is an essential cofactor for over 300 different enzymes. One magnesium-dependent enzyme is $\Delta 6$ -desaturase. Prostaglandin E_1 , a vasodilator and platelet inhibitor, is regulated by that enzyme. The recommended daily intake for magnesium for adult men and women over 31 years old is 420 mg and 320 mg, respectively. The mean average daily intakes in the United States was reported as 326 mg in Caucasian men, 237 mg in African American men, 237 mg in Caucasian women, and 177 mg in African American women.²⁷ Gaby reports that magnesium deficiency is one of the most common nutritional problems encountered in his general practice.²⁸ In a meta-analysis of 20 studies totaling 1220 participants, Jee et al reported that a dose-dependent BP reduction was observed with magnesium supplementation.²⁹

Vitamin B₆

Low plasma levels of vitamin B₆ are inversely related to major markers of inflammation and are independently associated with an increased risk of cardiovascular disease.³⁰ Vitamin B₆ is a cofactor for lysyl oxidase, which enhances arterial integrity by promoting the cross-linking of collagen and elastin.³¹ Vitamin B₆ is a cofactor that converts homocysteine to the amino acid methionine. Also, vitamin B₆ has numerous actions such as (1) being cofactor for the production of central neurotransmitters that reduce BP (serotonin, dopamine, norepinephrine, and epinephrine); (2) increasing cysteine for GSH production, which is an intracellular antioxidant that lowers BP; (3) having diuretic effects; and (4) reducing calcium-ion influx into arteries to reduce systemic vascular resistance. Vitamin B₆ is a natural calcium channel blocker, central alpha agonist, and diuretic.

Low serum vitamin B₆ levels are associated with hypertension.³² A deficiency of vitamin B₆ is associated with alcoholism, low dietary intakes, and impaired metabolism of the vitamin. A high prevalence of deficiency in the elderly has also been reported.

A study using a combination of folate (1 mg), vitamin B₁₂ (500 mcg) and vitamin B₆ (10 mg) for 2 years did not find a BP-lowering effect in older individuals³³ with elevated levels of homocysteine. In a separate study using 5 mg of folic acid plus 250 mg of vitamin B₆ over a 2-year period, van Dijk et al reported a BP-lowering effect of 3.7 mm Hg SBP and 1.9 mm Hg DBP.³⁴ Another study by Aybak et al showed lowered BP using high-dose vitamin B₆. This study comprised 9 normotensive participants and 20 participants with essential hypertension. The participants were treated for 4 weeks with vitamin B₆ at 5 mg/kg body weight/day. SBP fell from 167 ± 13 mm Hg to 153 ± 15 mm Hg ($P < .01$) and DBP fell from 108 ± 8.2 mm Hg to 98 ± 8.8 mm Hg ($P < .005$).³⁵

Vitamin D₃

Vitamin D₃ influences BP by its effects on calcium-phosphate metabolism, the renin-angiotensin system, the immune system, control of the endocrine glands, and endothelial dysfunction. The third National Health and Nutrition Examination Survey (NHANES II) showed that SBP was inversely and significantly correlated with 1,25(OH)₂D levels among 12 633 participants. The incidence of elevated BP was lower in individuals with vitamin D sufficiency. Vitamin D deficiency is common in the general population.³⁶

In one study, 34 vitamin D-deficient participants with type 2 diabetes were randomly assigned to receive a placebo or 100 000 IU of vitamin D₃. After 8 weeks, those participants in the vitamin D group had a mean SBP that was 14 mm Hg lower than the control group ($P = .001$).³⁷ In a group of 148 women with low vitamin D levels, administration of 1200 mg of calcium plus 800 IU vitamin D₃ per day reduced SBP at least 5 mm Hg as compared to controls.³⁸ The mechanisms may include:

Renin Activity. In individuals with arterial hypertension, renin activity has been inversely associated with 1,25(OH)₂D levels.³⁹ Via conversion of angiotensin, renin induces vasoconstriction.

Prostacyclin Production. Vitamin D₃ increases prostacyclin (PGI₂) production by vascular smooth-muscle cells.⁴⁰ PGI₂ inhibits platelet aggregation and increases vasodilation.

Increase in eNOS Activity. Vitamin D₃ has been shown to increase the activity of eNOS. Advanced glycation end products (AGEs) are formed via the nonenzymatic reactions of reducing sugars with free amino groups of nucleic acids, lipids, and proteins. AGEs have been shown to decrease the eNOS mRNA expression and enzyme activity by endothelial cells. At physiological concentrations, Vitamin D₃ as 1,25(OH)₂D has been shown to inhibit the effect of AGEs on eNOS production in a cell-culture system.⁴¹

Biotin

Biotin is considered a safe, water-soluble vitamin with no serious side effects, even when given in high doses. Oral doses of up to 5000 mcg per day for 2 years have been reported with no adverse effects.⁴² Although biotin deficiency is currently not a classic risk factor for hypertension, studies do suggest a probable role for biotin in vasodilation via the production of NO in the endothelium.

Biotin was investigated for hypertension in the stroke-prone, spontaneously hypertensive rat (SHRSP) strain.⁴³ The SHRSP strain is a salt-sensitive strain that demonstrates a high incidence of hypertension and stroke. Oral biotin administration containing 150 mcg biotin/kg was found to reduce SBP in the SHRSP in 2 weeks.

Biotin is known to increase the activity of soluble guanylate cyclase (sGC) and cGMP levels. Kinases that are sGC- and cGMP-dependent are involved in the relaxation

of smooth muscles and the lowering of BP. NO is known to mediate vasodilation via sGC activation. Biotin is known to be a direct activator of sGC. The proposed mechanism of action underlying the hypotensive effect of biotin in the SHRSP model was based upon NO-independent activation of sGC.

In vitro studies conducted using biotin at concentrations that were physiologically relevant observed that NO signaling depends on biotin in the lymphoid cell model. NO generation in the human lymphoid cells was mediated by increased expressions of eNOS.⁴⁴ The actual mechanism by which biotin increases the expression of eNOS is undetermined.

Taurine

Taurine is a conditionally essential amino acid that has clinically been shown to be effective in reducing BP. As a sulfonic amino acid, taurine inhibits apoptosis, inflammation, oxidative stress, and cell death while increasing NO generation in endothelial cells.⁴⁵ Humans are able to synthesize taurine from methionine and cysteine in the presence of vitamin B₆. Attenuation of both hemodynamic and stress-induced changes in catecholamine/sympathetic activity has been suggested to be affected by taurine. In the rat model, hypertension induced by the administration of ethanol for 4 weeks was prevented through supplementation with taurine at 1% of the diet by weight.⁴⁶

Fujita studied the effects of oral administration of 6 g of taurine per day for 4 weeks in 19 young participants with borderline hypertension. Participants treated with taurine decreased SBP by 9.0 ± 2.9 mm Hg ($P < .05$) and DBP by 4.1 ± 1.7 mm Hg ($P < .05$). Participants receiving taurine in this study also had a reduction of plasma epinephrine levels ($P < .05$).⁴⁷

Taurine and vitamin C have been shown to modify monocyte and endothelial dysfunction in young smokers. Endothelial-dependent vasodilation was found to be impaired in young smokers, who had an impaired release of NO and increased levels of endothelin-1. Endothelin-1 is a potent vasoconstrictor with a prolonged duration of action. Pretreatment of young smokers for 5 days with 2 g of vitamin C plus 1.5 g of taurine per day attenuated this response, as measured in cultured, peripheral blood, mononuclear cells.⁴⁸

Study Limitations

This study is limited by the length of the investigation. Although changes in BP are evident in a short period of time, we cannot extrapolate the long-term effects of nutritional supplementation on BP changes without further trials. Such studies also need larger numbers of patients. Although seven nutrients were used in the study, we do not know the interactions between all individual nutrients on BP. We additionally do not know if some patients were responding to one specific nutrient, or to more than one of the seven nutrients provided by the study.

Conclusion

Individually, micronutrients are recognized for lowering BP in hypertensive individuals. Nutrients often work optimally with cofactors, and thus, can be less powerful when acting independently than in combination. The expression of NO by eNOS is known to be regulated in part by the interaction of vitamin C, vitamin D, biotin, taurine, and polyphenols with low molecular weights, such as grape seed extracts.⁴⁹ Other essential nutrients, such as vitamin B₆ and magnesium, are known to regulate BP through various mechanisms. This study reports the significant reduction of SBP over a 4-week period with treatment that used a standardized blend of seven nutrients. Further studies using nutraceuticals are recommended to examine their effects on BP in individuals with hypertension. Larger groups and longer treatment periods are recommended for such studies.

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