Treatment of Hypertension with Nutrition and Nutraceutical Supplements: Part 2

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Introduction

This article continues a review of the role of nutrition and selected nutraceutical supplements, minerals, vitamins, anti-inflammatory agents, natural immune modulators, and antioxidants in the treatment of hypertension, begun in the prior issue of this journal.

Vitamin D

Vitamin D3 has variable blood pressure (BP)-lowering effects.^{1–23} Vitamin D may have an independent and direct role in the regulation of BP, insulin metabolism, and dysglycemia,^{5–17} but the results have not been consistent in prospective studies or in meta-analyses in which there has been little or no significant BP reduction.^{18–19,21,23} If the vitamin D level is <30 ng/mL, the circulating plasma renin activity (PRA) levels are higher, which increases angiotensin II and elevates BP.¹⁵ The lowest quartile of serum vitamin D has a 52% incidence of hypertension versus the highest quartile, which has a 20% incidence.¹⁵ Compared to a 25-hydroxyvitamin D > 30 ng/mL, a 25-hydroxyvitamin D < 20 ng/mL was associated with a greater hypertension risk (odds ratio [OR] = 1.225; *P* = 0.04).¹⁵ In another study, during a median follow-up of two years, 42.6% of the cohort developed hypertension.¹⁷ Compared to a 25-hydroxyvitamin D > 30 ng/mL, a 25-hydroxyvitamin D 20 ng/mL was associated with a greater risk of hypertension (OR = 1.225 [95% confidence interval (CI) 1.010–1.485]; *P* = 0.04).¹⁷ This meta-analysis, including seven prospective studies of 53,375 participants, showed a significant association between vitamin D deficiencies and incident hypertension (hazard ratio [HR] = 1.23; *P* = 0.002).¹⁷ A recent meta-analysis from eight randomized controlled trials (RCTs), with patients who received treatment with vitamin D for more than three months, showed that vitamin D supplementation slightly decreased systolic BP (SBP) by 1.964 mmHg (*P* = 0.016), but diastolic BP (DBP) did not change.¹⁹ Compared to placebo, there was also no statistical difference in SBP lowering by vitamin D supplementation.¹⁹ Vitamin D3 markedly suppresses renin transcription by

a vitamin D receptor-mediated mechanism via the juxtaglomerular apparatus, which alters electrolyte balance, volume, and BP.^{1,7} Vitamin D reduces asymmetric dimethyl arginine, suppresses pro-inflammatory cytokines, increases nitric oxide (NO), improves endothelial function and arterial elasticity, and decreases vascular smooth-muscle hypertrophy.^{8–15}

The hypotensive effect of vitamin D was inversely related to the pretreatment serum levels of 1,25 (OH)₂ D₃ and has additive BP reduction when used concurrently with antihypertensive medication.¹⁶ Black people have significantly higher rates of hypertension than white people, as well as lower circulating levels of 25-hydroxyvitamin D.²² In a three-month study of placebo, 1000, 2000, or 4000 IU of cholecalciferol per day, the difference in SBP between baseline and three months was +1.7 mmHg for those receiving placebo, –0.66 mmHg for 1000 IU/day, –3.4 mmHg for 2000 IU/day, and –4.0 mmHg for 4000 IU/day of cholecalciferol (–1.4 mmHg for each additional 1000 IU/day of cholecalciferol; *P* = 0.04). For each 1 ng/mL increase in plasma 25-hydroxyvitamin D, there was a significant 0.2 mmHg reduction in SBP (*P* = 0.02).²² There was no effect of cholecalciferol supplementation on DBP (*P* = 0.37). Vitamin D levels are lower in patients with non-dipping hypertension.²⁰ A vitamin D level of 60 ng/mL is recommended for optimal BP reduction and cardiovascular disease (CVD) risk reduction.^{1–4}

Vitamin B6 (Pyridoxine)

Low serum vitamin B6 (pyridoxine) levels are associated with hypertension in humans.^{1–4,24–28} High-dose vitamin B6 significantly lowered BP by 14/10 mmHg (*P* < 0.005) and serum catecholamine levels (*P* < 0.05) in a placebo-controlled study of 20 hypertensive subjects who were administered vitamin B6 at 5 mg/kg/day for four weeks.²⁵

In a placebo-controlled trial over 12 weeks, in which participants were given 800 mg lipoic acid and 80 mg pyridoxine, results showed that serum lipoic acid and pyridoxine, urinary albumin, serum malondialdehyde, and SBP decreased significantly in the supplement group compared to the placebo group

($P < 0.05$).²⁸ Serum NO increased in the supplement group compared to the placebo group ($P < 0.05$). No statistically significant differences were observed between the two groups in mean changes of serum endothelin-1 (ET-1), glucose, and DBP.²⁸

Vitamin B6 thus has similar action to central alpha agonists, diuretics, and calcium channel blockers (CCB).¹⁻⁴ The recommended dose is 200 mg/day orally at which no adverse effects have been reported related to neuropathy.¹⁻⁴

Flavonoids: Resveratrol and Pomegranate

Flavonoids (flavonols, flavones, and isoflavones) are potent free radical scavengers that prevent atherosclerosis, promote vascular relaxation, and have antihypertensive properties.²⁹⁻³⁹

Resveratrol administration to humans reduces augmentation index, improves arterial compliance, and lowers central arterial pressure when administered as 250 mL of either regular or dealcoholized red wine.³¹⁻³⁵ Aortic augmentation index fell 6.1% with the dealcoholized red wine and 10.5% with regular red wine. Central arterial pressure was reduced by dealcoholized red wine by 7.4 mmHg and by regular red wine by 5.4 mmHg. Resveratrol increases flow-mediated vasodilation in a dose-related manner, improves endothelial dysfunction, prevents uncoupling of endothelial nitric oxide synthase (eNOS), and blocks the effects of angiotensin II.³¹⁻³⁵ The recommended dose is 250 mg/day of trans-resveratrol.^{1-4,33}

Pomegranate (*Punica granatum*) reduces serum angiotensin-converting enzyme (ACE) activity by 36%, improves endothelial function, lowers BP, and reduces carotid intima-media thickness (IMT).^{1-3,36-39} A meta-analysis from eight RCTs showed significant reductions in both SBP (4.96 mmHg; $P < 0.001$) and DBP ($P = 0.021$) after 6 oz. of pomegranate juice consumption.³⁶

Lycopene

Lycopene consumption produces a significant reduction in BP, serum lipids, and oxidative stress markers.^{1-4,40-55} Dietary sources include grapefruit, watermelon, tomatoes, guava, pink apricots, and papaya.^{1-4,40-55} In patients with grade I hypertension, a tomato lycopene extract (10 mg lycopene/day) for two months lowered BP by 9/7 mmHg ($P < 0.01$).^{49,51} Tomato extract administered to 31 hypertensive subjects over three months lowered BP by 10/4 mmHg.⁵⁰ Patients on antihypertensive agents including angiotensin I-converting enzyme inhibitor (ACEI), CCB, and diuretics had an additional significant BP reduction of 5.4/3 mmHg over six weeks when administered a standardized tomato extract.⁵¹ A meta-analysis of the effect of lycopene on SBP showed a significant BP-reducing effect (mean SBP change $\pm$ SE: -5.60 ± 5.26 mmHg; $P = 0.04$).⁵⁴ The doses ranged from 10 to 25 mg/day of lycopene in these trials.⁵⁴ Other studies have not shown changes in BP with lycopene.⁵² The recommended daily intake of lycopene is 10–25 mg

in food or in a supplement form, but it is not clear which has the best effect on BP and CVD risk.⁵⁵ However, present data suggest that supplemental forms of lycopene are superior for BP reduction.⁵⁵

Coenzyme Q10 (ubiquinone)

Coenzyme Q10 (CoQ10; ubiquinone) has consistent and significant antihypertensive effects in hypertensive subjects.^{1-4,40-48,56-73} CoQ10 increases eNOS and NO and improves endothelial function and vascular elasticity.^{1-4,40-48,65,66} CoQ10 serum levels decrease with age, chronic disease, oxidative stress, dyslipidemia, coronary heart disease (CHD), hypertension, diabetes mellitus (DM), statin and beta-blocker use, exercise, and atherosclerosis.^{1-4,40-48,65,66,71} Compared to normotensive patients, essential hypertensive patients have a higher incidence of CoQ10 serum deficiency (39% vs. 6% of controls).^{1-4,59,68,71} In a 12-week randomized, double-blind, placebo-controlled trial of subjects with isolated systolic hypertension (165/81–82 mmHg), CoQ10 administered orally at 60 mg b.i.d. reduced SBP by 18 mmHg ($P < 0.01$) and DBP by 2.6 mmHg ($P =$ not significant [n.s.]).⁵⁸ The serum level increased by 2.2 μ g/dL ($P < 0.01$). There was a 55% response rate, defined as a reduction in SBP of > 4 mmHg. The responders had an average reduction in SBP of 26 mmHg.⁵⁸ The therapeutic serum level of CoQ10 should be 3 μ g/mL.^{1,14,56,59,67,68} This dose is usually 3–5 mg/kg/day of CoQ10.^{1-4,56,61,67,68,74} Combining a targeted intracellular cardiac CoQ10 (MitoQ10) and low-dose losartan provides additive therapeutic benefit, significantly attenuating development of hypertension, increasing NO levels, and reducing left ventricular hypertrophy in the spontaneously hypertensive stroke prone rat.⁷² In addition, MitoQ10 mediates a direct anti-hypertrophic effect on rat cardiomyocytes in vitro.

Patients with the lowest CoQ10 serum levels may have the best antihypertensive response to supplementation.^{1-4,58} The average reduction in BP is about 15/10 mmHg with office readings (range 11–17/8–10 mmHg)^{1-4,56-73} and 18/10 mmHg with 24-hour ambulatory BP monitoring (ABPM; $P < 0.0001$).^{59,73} The antihypertensive effect peaks at four weeks, then the BP remains stable during long-term treatment,^{1-4,58} but within two weeks after discontinuation of CoQ10, the antihypertensive effect dissipates.^{1-4,58} The reduction in BP and systemic vascular resistance are correlated with the pre- and post-treatment levels of CoQ10 and the percent increase in serum levels.^{1-4,58,59} About 50% of patients respond to oral supplemental CoQ10.^{1-4,58} Patients administered CoQ10 with enalapril have better 24-hour ABPM control compared to enalapril monotherapy and better endothelial function.⁶⁴ Approximately 50% of patients on antihypertensive drugs may be able to stop between one and three agents. A recent meta-analysis that suggested that CoQ10 did not reduce BP is seriously flawed and biased in its data selection.⁶² The literature is supportive of significant reductions in BP in human clinical trials.^{1-4,56-61,63-71,73} Adverse effects have not been seen in patients in the literature.^{1-4,56-61,63-71,73}

Alpha Lipoic Acid

Recent research has evaluated the role of alpha lipoic acid (ALA) in the treatment of hypertension, especially when it is part of metabolic syndrome.^{1-4,75-81} Lipoic acid reduces oxidative stress, inflammation, and serum aldehydes, closing calcium channels, which leads to vasodilation, improved endothelial function, and lower BP.^{1-4,75-81} Urinary albumin excretion is stabilized in DM subjects given 600 mg ALA compared to placebo for 18 months ($P < 0.05$).⁸⁰ In a double-blind crossover study of 36 patients with CHD given 200 mg lipoic acid with 500 mg acetyl-L-carnitine b.i.d. for eight weeks,⁷⁹ there was a 2% increase in brachial artery diameter and a decrease in SBP from 151 ± 20 to 142 ± 18 mmHg ($P < 0.03$) with no change in DBP.⁷⁹ However, patients with metabolic syndrome had a reduction in SBP from 139 ± 21 to 132 ± 15 mmHg ($P < 0.03$) and DBP from 76 ± 8 to 73 ± 8 mmHg ($P < 0.06$).⁷⁹ In a two-month double-blind crossover study of 40 patients with DM and stage I hypertension, quinapril 40 mg daily versus quinapril 40 mg with lipoic acid 600 mg daily, urinary albumin excretion was reduced by 30% with quinapril and 53% with quinapril with lipoic acid ($P < 0.005$), BP was reduced significantly by 10% in both groups, and flow-mediated dilation (FMD) increased 58% with quinapril and 116% with the combination ($P < 0.005$).⁷⁸ The Homeostatic Model Assessment of Insulin Resistance decreased 19% with quinapril and 40% with quinapril with lipoic acid ($P < 0.005$). The combined administration of lipoic acid and pyridoxine improves albuminuria in patients with diabetic nephropathy.⁸¹ The recommended dose is 100–200 mg/day of R-lipoic acid.

Pycnogenol

Pycnogenol is a bark extract from the French maritime pine that significantly reduces BP in human trials.^{1-4,40-48,82-90} Pycnogenol administered at 200 mg/day lowered SBP by 2.7 mmHg ($P < 0.05$) and DBP by 1.8 mmHg ($P = \text{n.s.}$).⁸¹ The antihypertensive effect is mediated by an ACEI effect, reductions in ET-1, and increases in NO and prostaglandins, which reduces inflammation, oxidative stress, and improves endothelial function.^{1-4,40-48,82-90} Other studies have shown reductions in BP and a decreased need for ACEI and CCB.^{1-4,82,83,85,87}

Garlic

Meta-analyses and clinical trials of garlic administration have shown consistent reductions in BP in both hypertensive patients on antihypertensive medication and those not on antihypertensive medication, with an average reduction in BP of 7–16/5–9 mmHg.⁹¹⁻¹⁰¹ Garlic is a vasodilator with ACEI activity and CCB activity. It also increases NO.^{1-4,40-48,96} In a randomized, double-blind, placebo-controlled trial over three months, 900 mg aged garlic extract with 2.4 mg S-allylcysteine

reduced SBP by 10.2 mmHg ($P = 0.03$).⁹³ In another randomized, double-blind, placebo-controlled trial of 81 pre-hypertensive and mild hypertensive patients given 300 mg garlic homogenate for 12 weeks, the BP reduction was 6.6–7.5/4.6–5.2 mmHg.⁹⁴ Aged garlic extract at 480 mg/day had the best BP reduction of 11.8 ± 5.4 mmHg ($P = 0.006$).⁹⁵ Garlic improves central BP, central pulse pressure, mean arterial pressure (MAP), augmentation pressure, pulse-wave velocity, and arterial stiffness.⁹⁹

Seaweed

Wakame seaweed (*Undaria pinnatifida*) is the most popular edible seaweed in Japan.¹⁰² A daily dose of 3.3 g dried wakame for four weeks significantly reduced BP by $14 \pm 3/5 \pm 2$ mmHg ($P < 0.01$).¹⁰³ In a study of 62 middle-aged male subjects with mild hypertension given a potassium-loaded, ion-exchanging sodium-adsorbing, potassium-releasing seaweed preparation, significant BP reductions occurred at four weeks on 12 and 24 g/day ($P < 0.01$).¹⁰⁴ The MAP fell 11.2 mmHg ($P < 0.001$) in sodium-sensitive subjects and 5.7 mmHg ($P < 0.05$) in sodium-insensitive subjects, correlating with PRA.

Seaweed and sea vegetables contain 771 minerals and rare earth elements, fiber, and alginate in a colloidal form.¹⁰²⁻¹⁰⁴ Wakame has ACEI activity from at least four parent tetrapeptides and possibly their dipeptide and tripeptide metabolites, especially those containing the amino acid sequence Val-Tyr, Ile-Tyr, Phe-Tyr, and Ile-Try in some combination.^{102,105,106} Its long-term use in Japan has demonstrated its safety.

Cocoa: Dark Chocolate

Dark chocolate (100 g) and cocoa with a high content of polyphenols (≥ 30 mg) significantly reduces BP in various meta-analyses and clinical prospective trials.^{1-4,40-48,107-118} In a meta-analysis of 173 hypertensive subjects given cocoa for two weeks, BP was lowered by 4.7/2.8 mmHg ($P = 0.002-0.006$).¹⁰⁷ Fifteen subjects given 100 g dark chocolate with 500 mg polyphenols for 15 days had a 6.4 mmHg reduction in SBP ($P < 0.05$).¹⁰⁸ Cocoa at a dose of 30 mg polyphenols lowered BP in pre-hypertensive and stage I hypertensive patients by 2.9/1.9 mmHg at 18 weeks ($P < 0.001$).¹⁰⁹ Two meta-analyses of 13 trials and 10 trials with a total of 297 patients found a significant reduction in BP of 3.2/2.0 mmHg and 4.5/3.2 mmHg, respectively.^{111,114} The BP reduction is the greatest in those with the highest baseline BP and those with at least 50–70% cocoa at doses of 6–100 g/day.^{1-4,107-111,114}

A meta-analysis in 2012 of 20 randomized, double-blind, placebo-controlled trials involving 856 mostly healthy participants found a statistically significant BP-reducing effect of flavanol-rich cocoa products compared to controls in short-term trials of 2–18 weeks' duration (mean difference in SBP = -2.8 mmHg, $P = 0.005$; mean difference in DBP = -2.2 mmHg, $P = 0.006$).¹¹⁸ The participants were given 30–

1080 mg flavanols ($M = 545.5$ mg) in 3.6–105.0 g of cocoa products per day in the active intervention group.¹¹⁸ Cocoa improves insulin resistance, NO production, and endothelial function in patients with or without hyperglycemia.^{108,114–117}

Melatonin

Melatonin demonstrates significant antihypertensive effects in humans in numerous randomized, double-blind, placebo-controlled trials as single therapy or in conjunction with antihypertensive medication.^{119–146} Melatonin also inhibits plasma A-II levels centrally and in peripheral tissues.^{40,132–134,138} Melatonin levels are reduced by shortened sleep cycles of less than six hours, shift work, being aged > 40 years, brief light exposure after darkness, trespass light, beta blockers, and benzodiazapines.¹³⁸ Melatonin lowers nocturnal BP in diabetic and non-diabetic hypertensive patients and in those with CHD, and improves the dipping pattern in patients with nocturnal non-dipping status.^{120–126,128,130}

In a randomized, double-blind, placebo-controlled crossover study, chronic administration (three weeks) of melatonin at 2.5 mg before bedtime in hypertensive men who were not taking any antihypertensive medication lowered nocturnal BP by 6/4 mmHg, reduced day–night amplitudes of SBP by 15% and DBP by 25%, improved sleep, and reduced cortisol levels.¹¹⁹ In a meta-analysis of randomized, double-blind, placebo-controlled trials that included 221 participants treated with controlled-release melatonin 2–5 mg/night for 7–90 days, there was a significant decrease in night BP of 6.1/3.5 mmHg ($P = 0.009$).¹⁴³

Grape Seed Extract

Grape seed extract (GSE) produces a significant reduction in BP in clinical trials and meta-analyses.^{1–4,147–151} GSE in variable doses and variable amounts of resveratrol was administered to subjects in nine randomized trials—a meta-analysis of 390 subjects—and demonstrated a significant reduction in SBP of 1.54 mmHg ($P < 0.02$) but no reduction in DBP.¹⁴⁷ A significant reduction in BP of 11/8 mmHg ($P < 0.05$) occurs with 300 mg/day of GSE in one month.¹⁴⁸ A meta-analysis in 2016 reviewed 16 clinical trials with 810 subjects.¹⁵⁰ There were significant reductions in BP with GSE of 6/3 mmHg ($P = 0.001$), especially in young patients and those with obesity or metabolic syndrome.¹⁵⁰ A single-center, randomized, two-arm, double-blinded, placebo-controlled, 12-week parallel study was conducted in 36 middle-aged adults with pre-hypertension.¹⁵¹ Subjects consumed a juice containing placebo or 300 mg/day GSE, 150 mg b.i.d. for six weeks preceded by a two-week placebo run-in and followed by a four-week no-beverage follow-up.¹⁵¹ GSE significantly reduced SBP by 5.6% ($P = 0.012$) and DBP by 4.7% ($P = 0.049$).¹⁵¹ BP returned to baseline after the four-week discontinuation period of the GSE beverage. The higher the initial BP, the greater was the response.

Dietary Nitrates and Nitrites: Beetroot Juice and Extract

The Mediterranean and DASH diets and the ingestion of fruits and vegetables rich in inorganic nitrate (NO_3^-) are effective methods for elevating vascular NO levels through formation of an NO_2^- intermediate that reduces BP and improves arterial compliance and endothelial function.^{40,152–163}

The pathway for NO generation involves the activity of facultative oral microflora and the gastric/enterosalivary cycle to facilitate the reduction of inorganic NO_3^- , ingested in the diet, to inorganic NO_2^- . This NO_2^- eventually enters the circulation where, through the activity of numerous and distinct NO_2^- reductases, it is chemically reduced to NO.^{40,152,153} Dietary consumption of raw or cooked beets, beet juice or extract, or dark green leafy vegetables (kale and spinach) are concentrated sources of inorganic nitrates. This is the alternate pathway to the arginine NO/eNOS pathway mediated through eNOS. Beet juice at a dose of 250 mL/day reduces BP within 30–60 min in normotensive, pre-hypertensive, or mild hypertensive subjects.^{154,155} A meta-analysis of randomized, double-blind, placebo-controlled trials shows that daily beetroot juice consumption of 5.1–45 mmol (321–2790 mg) over a period of 2 h to 15 days is associated with dose-dependent changes in SBP (mean reduction = -4.4 mmHg; $P < 0.001$).¹⁵⁶ A blinded placebo-controlled crossover study of an orally disintegrating beet extract with folic acid lozenge that generates NO in the oral cavity evaluated the effects on BP response, endothelial function, and vascular compliance in 30 unmedicated hypertensive patients with an average baseline BP of $144 \pm 3/91 \pm 1$ mm Hg.¹⁵⁷ Nitrate supplementation versus placebo resulted in a significant decrease of 4/5 mmHg ($P < 0.002$) from baseline after 20 min. In addition, there was a further significant reduction of 6 mmHg in both systolic and diastolic pressure after 60 min ($P < 0.0001$ vs. baseline). After half an hour of a single dose, there was a significant improvement in vascular compliance as measured by the augmentation index and, after four hours, a statistically significant improvement in endothelial function as measured by the EndoPAT (Itamar Medical, Franklin, MA).¹⁵⁷ In another randomized, double-blind, placebo-controlled study of 68 drug-naïve and treated patients with hypertension, a daily dietary supplementation was given for four weeks with either dietary nitrate (250 mL daily as beetroot juice) or a placebo (250 mL daily as nitrate-free beetroot juice) after a two-week run-in period and followed by a two-week wash-out.¹⁵⁸ Daily supplementation with dietary nitrate was associated with a reduction in BP measured by three different methods. There was a mean reduction in clinic BP of 7.7/2.4 mmHg (3.6–11.8/0.0–4.9; $P < 0.001$ and $P = 0.050$). Twenty-four-hour ambulatory BP was reduced by 7.7/5.2 mmHg (4.1–11.2/2.7–7.7; $P < 0.001$ for both). Home BP was reduced by 8.1/3.8 mmHg (3.8–12.4/0.7–6.9; $P < 0.001$ and $P < 0.01$).¹⁵⁸ There was no evidence of tachyphylaxis, and the study supplement was well tolerated. Endothelial

function improved by $\sim 20\%$ ($P < 0.001$) and arterial stiffness was reduced by 0.59 m/s (0.24–0.93; $P < 0.01$) after dietary nitrate consumption with no change after placebo.¹⁵⁸ In a randomized crossover study of 24 hypertensive subjects, raw beet juice was administered for two weeks followed by cooked beets.¹⁶¹ After two weeks, both groups had a washout for two weeks and then switched to the alternative treatment. Each participant consumed 250 mL/day of beet juice or 250 g/day of cooked beets. FMD was significantly ($P < 0.05$) increased, and SPB and DBP were significantly ($P < 0.05$) decreased with beet juice and cooked beet.¹⁶¹

Based on these studies, there is a dose-related response to SBP, DBP, endothelial function, and other vascular parameters with beet juice, beet extract, and raw and cooked beets.^{152–163} The consumption of dietary nitrate at 0.1 mmol/kg of body weight per day (high intake of fruit and vegetables at four to six servings a day) reduces SBP and DBP by about 3.5–4.0 mmHg, and this effect is potentiated by vitamin C and polyphenols.^{152–163} Vegetables are the primary source of nitrates (80–85%).^{162,163} About 500 mg beetroot juice with 45 mmol/L or 2.79 g/L of inorganic nitrate lowers BP by 10.4/8.1 mmHg and increases FMD by 30%.^{162,163} Beetroot tends to be dosed based on the nitrate content, with around 0.1–0.2 mmol/kg (6.4–12.8 mg/kg) being the target for nitrate consumption. This is about 436 mg for a 150 lb person, which is comparable to half a kilogram (500 g) of the beetroots themselves (wet weight).^{162,163}

Tea

Green tea, black tea, and their respective extracts of active components have demonstrated a reduction in BP in human clinical trials and meta-analysis.^{164–175} In a randomized, double-blind, placebo-controlled trial of 379 hypertensive subjects given green tea extract (GTE) 370 mg/day for three months, BP was reduced significantly by 4/4 mmHg.¹⁶⁸

A meta-analysis of regular consumption of either green or black tea for 4–24 weeks (two to six cups per day) reduced BP significantly. Green tea lowered SBP by 2.1 mmHg and DBP by 2.0 mmHg, while black tea reduced SBP by 1.4 and DBP by 1.1 mmHg.¹⁶⁴ A small four-week randomized, double-blind, placebo-controlled crossover trial of 21 women administered 1500 mg GTE (containing 780 mg polyphenols) or a matching placebo for four weeks, with a washout period of two weeks between treatments, had significant reductions in SBP.¹⁷² The 24-hour ABPM showed an overall decrease in SBP of 3.6 mmHg, daytime reduction of 3.61 mmHg, and nighttime reduction of 3.9 mmHg.¹⁷² There was no reduction in DBP. A meta-analysis of 10 trials with 834 subjects noted a reduction in BP of 2.36/1.77 mmHg with green and black tea in three months. The best results were with decaffeinated tea. The required amount is about 500 mg flavonoid content (two cups of tea/day).¹⁷⁵ Green tea lowers systemic vascular resistance and induces microvascular vasodilation.^{173,174}

L-Carnitine and Acetyl-L-Carnitine

Carnitine has mild systemic antihypertensive effects by upregulation of eNOS and inhibition of the renin–angiotensin–aldosterone system (RAAS).^{1–4,176–186} Endothelial function, NO, and oxidative defense are improved, while oxidative stress and BP are reduced.^{176–180}

Human studies on the effects of L-carnitine and acetyl-L-carnitine are limited, with minimal to no change in BP.^{1–4,181–186} In patients with metabolic syndrome, acetyl-L-carnitine at 1 g b.i.d. over eight weeks improved dysglycemia and reduced SBP by 7–9 mmHg, but DBP was significantly decreased only in those with higher glucose levels.¹⁸⁷ Low carnitine levels are associated with a non-dipping BP pattern in type 2 DM.¹⁸⁶ The clinical role of carnitine in hypertension and CVD must be carefully evaluated, as carnitine may increase trimethylamine oxidase (TMAO) via the gut microbiome. Elevated TMAO is associated with atherosclerosis and CHD.¹⁸⁷ Doses of 2–3 g b.i.d. are recommended if carnitine is used.^{1–4}

Fiber

Clinical trials with various types of fiber to reduce BP have been inconsistent.^{1–4,188–193} Soluble fiber, guar gum, guava, psyllium, flax seed, and oat bran may reduce BP and decrease the need for antihypertensive medication in hypertensive subjects, diabetic subjects, and hypertensive-diabetic subjects, especially when these fibers are incorporated into the Mediterranean diet.^{1–4,188–193} In a meta-analysis, dietary fiber intake was associated with a significant 1.65 mmHg reduction in DBP, but a nonsignificant 1.15 mmHg reduction in SBP.¹⁸⁸ However, a significant reduction in both SBP and DBP was observed in trials conducted among patients with hypertension (5.95/4.20 mmHg) and in trials with a duration of eight weeks or more (BP 3.12/2.57 mmHg).¹⁸⁸ In a recent meta-analysis of 14 RCTs, flaxseed, which is a rich dietary source of α -linolenic acid, lignans, and fiber, was shown to lower BP by 1.8/1.6 mmHg ($P = 0.003$).¹⁹³

Sesame

Sesame has been shown to reduce BP in several small, randomized, placebo-controlled human studies over 30–60 days.^{194–202} Sesame lowers BP alone^{203–207} or in combination with nifedipine,^{206,208} diuretics, or beta blockers.^{203,207} In a group of 13 mild hypertensive subjects, 60 mg sesamin for four weeks lowered SBP by 3.5 mmHg ($P < 0.044$) and DBP by 1.9 mmHg ($P < 0.045$).²⁰⁴ Black sesame meal at 2.52 g/day over four 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.²⁰⁵ Sesame oil at 35 g/day significantly lowered central BP within one hour and also maintained BP reduction chronically in 30 hypertensive subjects, and reduced heart rate, arterial stiffness, augmentation index, pulse wave velocity, and

high sensitivity C-reactive protein (hsCRP).²⁰² Also, sesame oil improved NO and antioxidant capacity and decreased ET-1.²⁰² In addition, sesame lowers serum glucose, hemoglobin A1C, and low-density lipoprotein cholesterol, increases high-density lipoprotein cholesterol, reduces oxidative stress markers, and increases glutathione, superoxide dismutase, glutathione peroxidase, catalase, and vitamins C, E, and A.^{203,205–208} The active ingredients are natural ACEI's such as sesamin, sesamol, sesaminol glucosides, and furofuran lignans, which also suppress NF- κ B and inflammatory cytokine production.^{209,210} All of these effects lower inflammation, decrease oxidative stress, improve oxidative defense, improve endothelial function, vasodilate, and reduce BP.^{209,210}

Hesperidin

Hesperidin at 135 mg/day significantly lowered DBP by 3–4 mmHg ($P < 0.02$) and improved microvascular endothelial reactivity in 24 obese hypertensive male subjects in a randomized, controlled crossover study over four weeks for each of three treatment groups consuming 500 mL orange juice, hesperidin, or placebo.²¹¹

N-Acetylcysteine

N-acetylcysteine (NAC) and L-arginine (ARG) in combination reduces endothelial activation and BP in hypertensive patients with and without type 2 DM.^{212–215} In 24 subjects with type 2 DM and hypertension treated for six months with placebo or NAC 600 mg b.i.d. with ARG 1200 mg b.i.d., both SBP and DBP were significantly reduced ($P = 0.05$).²¹² NO and endothelial post-ischemic vasodilation increased.²¹² NAC increases NO via interleukin 1b and increases iNOS mRNA, increases glutathione by increasing cysteine levels, reduces the affinity for the AT1 receptor by disrupting disulfide groups, blocks the L type calcium channel, lowers homocysteine, and improves carotid IMT.^{212–215} The recommended dose is 500–1000 mg b.i.d.

Hawthorn (*Crataegus species*)

Hawthorn berry extract has been used for centuries for the treatment of hypertension, CHF, and other cardiovascular diseases, but studies are limited and are not convincing of any significant clinical responses.^{216–220} A recent four-period crossover design, dose–response study of 21 subjects with prehypertension or mild hypertension over three and a half days did not show changes in FMD or BP on standardized extract 1000, 1500, or 2500 mg doses.²¹⁶ Hawthorn showed non-inferiority of ACEI and diuretics in the treatment of 102 patients with NYHC II CHF over eight weeks.²¹⁸ Patients with hypertension and type 2 DM on medication for BP and DM who were randomized to 1200 mg hawthorn extract for 16 weeks showed significant reductions in DBP of 2.6 mmHg ($P = 0.035$).²¹⁹ Thirty-six mildly hypertensive patients adminis-

tered 500 mg hawthorn extract for 10 weeks showed a nonsignificant trend in DBP reduction ($P = 0.081$) compared to placebo.²²⁰ Hawthorn acts like an ACEI, beta blocker, CCB, and diuretic. More studies are needed to determine the efficacy, long-term effects, and dose of hawthorn for the treatment of hypertension.

Quercetin

Quercetin is an antioxidant flavonol found in apples, berries, and onions that reduces BP in hypertensive individuals,^{221–223} but the hypotensive effects do not appear to be mediated by changes in hsCRP, tumor necrosis factor alpha, ACE activity, ET-1, NO, vascular reactivity, or FMD.²²¹ Quercetin inhibits CYP 3A4 and should be used with caution in patients on drugs metabolized by this cytochrome system.^{221–223} Quercetin was administered to 12 hypertensive men at an oral dose of 1095 mg with a reduction in mean BP of 5 mmHg, SBP by 7 mmHg, and DBP by 3 mmHg.²²¹ Forty-one pre-hypertensive and stage I hypertensive subjects were enrolled in a randomized, double-blind, placebo-controlled, crossover study with 500 mg quercetin per day versus placebo.²²² In the stage I hypertensive patients, BP was reduced by 7/5 mmHg ($P < 0.05$).²²² Quercetin administered to 93 overweight or obese subjects at 150 mg/day (plasma levels of 269 nmol/L) over six weeks lowered SBP by 2.9 mmHg in the hypertensive group and by up to 3.7 mmHg in patients aged 25–50 years.²²³ The recommended dose of quercetin is 500 mg b.i.d.

Probiotics

Gut dysbiosis in hypertension is characterized by a gut microbioma that is less diverse with an increased Firmicutes/Bacteroidetes ratio, a decrease in acetate- and butyrate-producing bacteria, and an increase in lactate-producing bacterial populations. There are several meta-analyses of humans that support the role of probiotic supplementation to reduce BP.^{224–227}

One meta-analysis of RCTs suggested that consuming probiotics results in a modest lowering of BP with a potentially greater effect with an elevated baseline BP, when multiple species of probiotics are consumed, the duration of the intervention is eight weeks or more, and the daily dose is $\geq 10^{11}$ colony-forming units.²²⁵

Another meta-analysis of 14 RCTs, involving 702 participants, showed that compared to placebo, probiotic fermented milk produced a slight but significant reduction in BP of 3.1/1.1 mmHg. Subgroup analyses suggested a slightly greater effect on SBP in hypertensive participants than in normotensive participants.²²⁴ In a meta-analysis of 11 eligible RCTs ($n = 641$), probiotic consumption significantly decreased SBP (weighted mean difference = -3.28 mmHg; 95% CI -5.38 to -1.18) and DBP (weighted mean difference = -2.13 mmHg; 95% CI -4.5 to 0.24), in type 2 DM patients compared to placebo.²²⁶ Hypertension may be caused by many factors, including hypercholesterolemia, chronic inflammation, and inconsistent modulation of the RAAS that are modified by probiotics.^{227–229}

Table 1. An Integrative Approach to the Treatment of Hypertension

Intervention category	Therapeutic intervention	Daily intake
Diet characteristics	DASH I, DASH II-Na ⁺ , or PREMIER diet	Diet type
	Sodium restriction	1500 mg
	Potassium	5000–10,000 mg
	Potassium/sodium ratio	> 4:1
	Magnesium	1000 mg
	Zinc	50 mg
Macronutrients	Protein: total intake from non-animal sources, organic lean or wild animal protein, or coldwater fish	30% of total calories, 1.5–1.8 g/kg body weight
	Whey protein	30 g
	Soy protein (fermented sources are preferred)	30 g
	Sardine muscle concentrate extract	3 g
	Milk peptides (VPP and IPP)	30–60 mg
	Fat:	30% of total calories
	Omega-3 fatty acids	2–3 g
	Omega-6 fatty acids	1 g
	Omega-9 fatty acids (MUFA)	4 tbsp (40 g) of EVOO or nuts
	Saturated fatty acids from wild game, bison, or other lean meat	<10% total calories
	Polyunsaturated to saturated fat ratio	> 2.0
	Omega-3 to omega-6 ratio	1.1–1.2
	Synthetic <i>trans</i> fatty acids	None (completely remove from diet)
	Nuts in variety	4 servings
	Carbohydrates: as primarily complex carbohydrates and fiber	40% of total calories
	Oatmeal or	60 g
	Oatbran or	40 g
	Beta-glucan or	3 g
	Psyllium	7 g
Specific foods	Garlic as fresh cloves or aged garlic extract	4 fresh cloves (4 g) or 600 mg aged garlic extract taken b.i.d.
	Sea vegetables, specifically dried wakame	3.0–3.5 g
	Lycopene as tomato products, guava, watermelon, apricots, pink grapefruit, papaya or supplements	10–20 mg
	Dark chocolate	100 g
	Pomegranate juice or seeds	8 oz or one cup
	Sesame	60 mg sesamin or 2.5 g sesame meal
	Beet juice	500 g
	Green tea or EGCG extract	60 oz of 500 mg b.i.d.
	Carnitine	2–6 g/day
Exercise	Aerobic	20 min/day at 4200 KJ/week
	Resistance	40 min/day

(continued)

Table 1. An Integrative Approach to the Treatment of Hypertension (Continued)

Intervention category	Therapeutic intervention	Daily intake
Weight reduction	Body mass index <25 kg/m ²	Lose 1–2 lbs per week and increase the proportion of lean muscle
	Waist circumference:	
	<35 inches for women	
	<40 inches for men	
	Total body fat:	
	<22% for women	
	<16% for men	
Other lifestyle recommendations	Alcohol restriction:	<20 g/day
	Among the choice of alcohol, red wine is preferred due to its vasoactive phytonutrients	Wine <10 oz
		Beer <24 oz
		Liquor <2 oz
	Caffeine restriction or elimination depending on CYP 1A2 450 SNP	<100 mg/day
	Tobacco and smoking	Stop
Medical considerations	Medications that may increase blood pressure	Minimize use when possible, such as by using disease-specific nutritional interventions
Supplemental foods and nutrients	Alpha lipoic acid with biotin	100–200 mg b.i.d.
	Amino acids:	
	Arginine	2 g b.i.d.
	Carnitine	1–2 g b.i.d.
	Taurine	1–3 g b.i.d.
	Chlorogenic acids	150–200 mg
	Coenzyme Q10	100 mg once to twice daily
	Grape seed extract	300 mg
	Hawthorne extract	500 mg b.i.d.
	Melatonin (long acting)	3 mg
	NAC	500 mg b.i.d.
	Olive leaf extract (oleuropein)	500 mg b.i.d.
	Pycnogenol	200 mg
	Quercetin	500 mg b.i.d.
	Probiotics	10 ¹¹ CFU
	Resveratrol (<i>trans</i>)	250 mg
	Vitamin B6	100 mg once to twice daily
	Vitamin C	250–500 mg b.i.d.
	Vitamin D3	Dose to raise 25-hydroxyvitamin D serum level to 60 ng/mL
	Vitamin E as mixed tocopherols	400 IU

EVOO, extra virgin olive oil.

Clinical Considerations

A comprehensive clinical approach to the categories and clinical use of nutraceutical supplements is detailed in tables 1 and 2 of Part 1.²³⁰ Several of the strategic combinations of nu-

traceutical supplements with antihypertensive drugs have been shown to lower BP more than the medication alone.^{1–4} These are:

- Pycnogenol with ACEI
- Lycopene with various antihypertensive medication

- R-Lipoic acid with ACEI
- Vitamin C with CCB
- N-acetylcysteine with arginine
- Garlic with ACEI, diuretics, and beta blockers
- CoQ10 with ACEI and CCB

Many antihypertensive drugs may cause nutrient depletions that can actually interfere with their antihypertensive action or cause other metabolic adverse effects that manifest through the laboratory results with clinical symptoms.^{231,232} Diuretics decrease potassium, magnesium, phosphorous, sodium, chloride, folate, vitamin B6, zinc, iodine, and Co Q10, increase homocysteine, calcium, and creatinine, and elevate serum glucose by inducing insulin resistance. Beta blockers reduce CoQ10, and ACEI and ARBs reduce zinc.^{231,232}

Clinical monitoring of BP is required, as well as patient awareness that dietary and supplemental interventions need to be taken as consistently as medication. Additional laboratory tests can inform clinical decision making such as the measurement of intracellular micronutrients in lymphocytes, antioxidant capacity, oxidative stress, inflammation biomarkers such as hsCRP, PRA, and serum aldosterone, followed by repletion of all micronutrient depletions with selected higher doses of nutritional supplements based on the clinical studies that have been reviewed.²³³

Conclusion

Derangements in vascular biology such as endothelial, vascular, and cardiac smooth-muscle dysfunction play a primary and pivotal role in the initiation and perpetuation of hypertension. Nutrient–gene interactions and epigenetics are predominant factors in promoting beneficial or detrimental effects in cardiovascular health and hypertension. Oxidative stress, inflammation, and vascular immune dysfunction initiate and propagate hypertension and cardiovascular disease.

Nutrition, natural whole foods, nutraceutical supplements, antioxidants, anti-inflammatory agents, and vitamins and minerals can prevent, control, and treat hypertension through numerous vascular biology mechanisms and may mimic the effects of the various antihypertensive drug classes. There is a role for the selected use of single and combined nutraceutical supplements, vitamins, antioxidants, and minerals in the treatment of hypertension based on prospective randomized placebo-controlled studies and meta-analyses as a complement to optimal nutrition and other lifestyle modifications. A clinical approach that incorporates optimal nutrition with scientifically proven nutraceutical supplements, exercise, weight reduction, smoking cessation, alcohol and caffeine restriction, and other lifestyle strategies can be systematically and successfully incorporated into clinical practice for the prevention and treatment of hypertension. ■

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