Treatment of Hypertension with Nutrition and Nutraceutical Supplements: Part 1

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Introduction

Cardiovascular disease (CVD) remains the leading cause of death in the United States. Hypertension is one of the top five risk factors for coronary heart disease (CHD) and CVD and remains the most common reason for visits to primary care physicians, with antihypertensive drugs costing >U.S.\$20 billion annually.^{1–19} There are >100 million people in the United States with hypertension based on new hypertension guidelines.¹⁹ In numerous clinical trials, pharmacotherapy will control blood pressure (BP) and reduce stroke, CHD, myocardial infarction (MI), congestive heart failure (CHF), and renal disease.^{16,17} However, some hypertensive patients either refuse to take drugs or prefer to treat with nutrition or nutritional supplements.^{1–20}

Hypertension is a consequence of micro- and macronutrient insufficiencies, abnormal vascular biology, reduced bioavailability of nitric oxide (NO), and the three finite vascular responses to vascular injury: inflammation, oxidative stress, and vascular immune dysfunction with activation for cell-mediated immunity (see Fig. 1).^{2–5,11–14} These abnormalities coexist and interact with genetics, epigenetics, nutrient–gene expression, and other environmental and lifestyle factors.^{2–5,11–14} Hypertension is initially the expected and normal response to these infinite insults from the environment (including microbes, heavy metals, biochemical, biohumoral, and biomechanical issues, lipids, glucose, obesity, smoking, homocysteine, and many others) to the endothelium, but chronic dysregulation of this response associated with gene expression patterns leads to a complex series of vascular events in which the vascular system becomes an innocent bystander.^{2–5,11–14} Hypertension is one of several responses of the blood vessel to endothelial dysfunction (ED). Cardiac smooth-muscle and vascular dysfunction and abnormalities of both microvascular function and structure precede the development of hypertension by decades. This consequently leads to vascular and cardiac hypertrophy, remodeling, functional and structural network rarefaction, decreased vasodilatory reserve, altered media-to-lumen ratio, stiffness, loss of arterial elasticity, fibrosis, increased pulse

pressure, elevated pulse wave velocity (PWV), and increased augmentation index (see Fig. 2).^{2–5,11–14} Significant functional and then structural microvascular impairment begins before elevations in BP in normotensive offspring of hypertensive parents.^{2–5,11–14}

As the BP increases, a bidirectional feedback occurs between the increased BP and the endothelial and vascular smooth-muscle dysfunction that exacerbates and perpetuates the cardiovascular functional and structural abnormalities. Macronutrients and micronutrients are crucial in the regulation of BP and subsequent cardiovascular target organ damage (TOD).^{2–5,11–14} Certain nutrient deficiencies are more common in patients with hypertension than in the general population.^{2–5,11–14} The appropriate measurement, interpretation, and treatment of these nutrient deficiencies may effectively lower BP and improve ED, vascular and cardiac functional and structural abnormalities, and cardiovascular events.^{2–5,11–14}

This two-part article will primarily review the role of nutrition and selected nutraceutical supplements, minerals, vitamins, anti-inflammatory agents, natural immune modulators, and antioxidants in the treatment of hypertension.

Epidemiology and Pathophysiology

The human genome is 99.9% identical to our Paleolithic ancestors, but the ability of the genome to adapt to changes in modern nutrition and macronutrient and micronutrient intake explains some of the reasons for the increase in CVD (see Table 1).²¹ Derangements in vascular biology assumes a pivotal role in the initiation and perpetuation of hypertension.^{2–5,11–14} Reactive oxygen species (ROS) coupled with impaired oxidative defense, inflammatory mediators, vascular immune dysfunction, and loss of NO bioavailability contribute to hypertension through complex nutrient–gene interactions.^{2–5,11–14,22–32} The high sodium/potassium ratio of modern diets, the reduced intake of magnesium, fiber, protein, and omega-3 fatty acids (FA) with increased consumption of omega-6 FA, saturated FA, and trans FA have contributed to hypertension.^{2–5,11–14,21}

Figure 1. Finite responses to vascular injury. Infinite insults to the blood vessel result in only three finite responses of inflammation, oxidative stress, and vascular immune dysfunction. These finite responses result in endothelial dysfunction and vascular smooth-muscle dysfunction, which leads to clinical cardiovascular disease.

Oxidative Stress, Inflammation, and Vascular Immune Dysfunction

Oxidative stress is an imbalance of ROS with a decrease in antioxidant defenses that contributes to hypertension in humans based on genetics and environment.^{2-5,11-14,23-37} The predominant ROS produced is superoxide anion, which is generated by numerous cellular sources that uncouple endothelium-derived NO synthase (U-eNOS) and reduce NO bioavailability. This results in ED and increased BP.^{24,27} Antioxidant deficiency and excess free radical production have been implicated in human hypertension in epidemiologic, observational, and interventional studies.²⁹⁻³¹ Free radicals degrade NO, influence eicosanoid metabolism, and increase catecholamine levels in serum and urine.^{2-5,11-14,24,26,27} The interrelations of neurohormonal systems, oxidative stress, and CVD is shown in Figure 3.

Acute and chronic inflammation with abnormal vascular immune responses and involvement of pattern recognition receptors (PRR) and Toll-like receptors (TLR) are involved in

Figure 2. Infinite insults and the three finite vascular responses. Infinite insults and the three finite vascular responses of inflammation, oxidative stress, and vascular immune dysfunction lead to endothelial dysfunction and cardiac and vascular dysfunction.

Table 1. Contrasting the Intake of Nutrients Involved in Vascular Biology: Evolutionary Nutritional Impositions^a

Nutrient	Paleolithic intake	Modern intake
Potassium	> 10,000 meq/day (256 g)	150 meq/day (6 g)
Sodium	<50 mmol/day (1.2 g)	175 mmol/day (4 g)
Sodium/potassium ratio	<0.13/day	> 0.67/day
Fiber	> 100 g/day	9 g/day
Protein	37%	20%
Carbohydrate	41%	40–50%
Fat	22%	30–40%
Polyunsaturated/saturated fat ratio	1.4	0.4

^aEaton SB, Eaton SB III, Konner MJ. Paleolithic nutrition revisited: A twelve-year retrospective on its nature and implications. *Eur J Clin Nutr* 1997;51:207–216.

hypertension.^{2–5,11–14,33–50} Low levels of interleukin 10 (IL-10) and increased levels of high sensitivity C-reactive protein (hs-CRP), along with numerous inflammatory cytokines such as interleukins (IL-6, IL-1 β , IL-2, and IL-8), and tumor necrosis factor alpha (TNF- α) are excellent markers for hypertension and hypertensive-related TOD, such as CHD, CHF, and increased carotid intimal medial thickness (IMT).^{2–5,11–14,33–50} Elevated hs-CRP is both a risk marker and risk factor for hypertension and CVD.^{2,38,39} Increases in hs-CRP of > 3 μ g/mL may increase BP rapidly in proportion to the serum hs-CRP level.^{38,39} NO and eNOS are inhibited by CRP.^{38,39} The angiotensin 2 receptor (AT2R), which increases NO when stimulated, normally counterbalances AT1R, but it is down-regulated or blocked by CRP.^{2,38,39} Angiotensin II (A-II) is inflammatory, atherogenic, increases oxidative stress and

vascular immune dysfunction that involves T and B cells and the innate and adaptive immune system, and upregulates many of the cytokines.^{2,44,49}

Innate and adaptive immune responses induce hypertension by numerous mechanisms that include A-II, antibodies to the AT1R, pro-inflammatory cytokine and chemokine production, PRR and TLR activation, central nervous system (CNS) stimulation, and renal damage.^{2–4,35,36,40–50} Monocytes cross the endothelial lining, invade the subintimal layer, and transform into macrophages. The macrophages, along with various T-cell subtypes that regulate BP, cause vascular damage and promote vascular immune dysfunction.⁴¹ A-II activates immune cells in the arterial system and also in the CNS.^{41,44,49} Activation of the AT1R and peroxisome proliferator-activated receptor gamma (PPAR- γ) receptors that are expressed on

Figure 3. The neurohormonal and oxidative stress systems with interactions on cardiac and vascular muscle. The sympathetic nervous system and therein angiotensin system induce vasoconstriction, hypertension, and cardiovascular disease. Endothelial dysfunction increases oxidative stress from peroxynitrite, and activation of neutrophils increases oxidative stress from hypochlorous acid. The clinical consequences are hypertension, atherosclerosis, coronary heart disease (CHD), cardiovascular disease (CVD), congestive heart failure, and arrhythmias.

Figure 4. The balance of cardiovascular disease. Cardiovascular disease is a balance of vascular injury and vascular repair. Nitric oxide balances the injury induced by angiotensin II, endothelin, and aldosterone. The endothelial progenitor cells repair the endothelium.^{205,206}

CD4+T lymphocytes release TNF- α , interferons, and interleukins within the vascular wall.^{41,50} IL-17 produced by T-17 cells may play a pivotal role in the genesis and perpetuation of hypertension caused by A-II.⁴¹

The Balance of Hypertension

Hypertension is a balance of vascular damage and repair that is mediated through the three finite responses. Vasoconstrictive

and atherogenic hormones such as A-II, endothelin, and aldosterone are also involved in the hypertensive response with arterial constriction and sodium and water retention that increases the intravascular volume (see Figs. 4 and 5).^{2-5,11-14} Vascular protection and repair is mediated by NO and bone marrow-derived endothelial progenitor cells (EPCs).^{2-5,11-14} The endothelium maintains communication and homeostasis between the circulating blood cells and the vascular media. It accomplishes this by modulation of the permeability, contractile state, proliferation, migratory response, and the redox state in the vascular media. It also modulates platelet function, coagulation, monocyte and leukocyte adhesion, inflammation, oxidative stress, and immune responses in the blood (see Figs. 6 and 7).^{2-5,11-14}

Treatment of Hypertension with Nutritional Supplements

A large number of nutraceutical supplements, antioxidants, vitamins, minerals, and natural compounds in food produce physiologic effects that mimic specific classes of antihypertensive medications, improve vascular biology, and decrease BP.²⁻¹⁴ These natural compounds are pluripotent but may also be classified into the major antihypertensive drug groups, which assists clinicians in making a logical transition from a drug of a certain antihypertensive class to a supplement with a similar but broader mechanism of action. These classes include diuretics, beta blockers, central alpha agonists, calcium

Figure 5. The three finite responses and vascular biology play a key role between CHD risk factors, endothelial and cardiovascular dysfunction, and CVD.²⁰⁶

Figure 6. The blood vessel structure: endothelium, smooth muscle, and adventitia. The endothelium communicates with the luminal blood elements and the vascular media.^{205,206}

channel blockers (CCB), angiotensin converting enzyme inhibitors (ACEI), and angiotensin receptor blockers (see Table 2).²⁻¹⁴ Numerous clinical nutrition studies have demonstrated the efficacy of dietary interventions for the prevention and treatment of hypertension, including Dietary Approaches to

Stop Hypertension (DASH 1 and DASH 2), the Mediterranean diet (MedDiet), Trials of Hypertension Prevention (TOHP 1 and TOHP 2), Trial of Nonpharmacologic Intervention in the Elderly (TONE), Treatment of Mild Hypertension (TOMHS), INTERMAP, INTERSALT, Premier, Vanguard, and others.^{2-5,10-14,51,52}

Figure 7. Vascular endothelium: strategic anatomical position to maintain vascular homeostasis. The endothelium has a strategic location and function to maintain communication and homeostasis between the circulating blood elements and the vascular smooth muscle.^{205,206}

Table 2. Natural Antihypertensive Compounds Categorized by Antihypertensive Class

Antihypertensive therapeutic class (alphabetical listing)	Foods and ingredients listed by therapeutic class	Nutrients and other supplements listed by therapeutic class
Angiotensin converting enzyme inhibitors	Egg yolk	Melatonin
	Fish (specific):	Omega-3 fatty acids
	Bonito	Pomegranate
	Dried salted fish	Probiotics
	Fish sauce	Pycnogenol
	Sardine muscle/protein	Quercetin
	Tuna	Zinc
	Garlic	
	Gelatin	
	Hawthorne berry	
	Isoflavones/flavonoids	
	Milk products (specific):	
	Casein	
	Sour milk	
	Whey (hydrolyzed)	
	Protein	
	Sake	
	Sea vegetables (kelp)	
	Seaweed (wakame)	
	Sesame (also ET1)	
	Wheat germ (hydrolyzed)	
	Zein (corn protein)	
Angiotensin receptor blockers	Celery	Coenzyme Q10
	Fiber	Gamma linolenic acid
	Garlic	NAC
	MUFA	Oleic acid
		Resveratrol
		Potassium
		Taurine
		Vitamin C
		Vitamin B6 (pyridoxine)
Beta blockers	Hawthorne berry	
Calcium channel blockers	Celery	Alpha lipoic acid
	Garlic	Calcium
	Hawthorn berry	Magnesium (PGE, NO)
	MUFA	N-acetyl cysteine
		Oleic acid
		Omega-3 fatty acids:
		Eicosapentaenoic acid
		Docosahexaenoic acid
		Taurine
		Vitamin B6
<i>(continued)</i>		

Table 2. Natural Antihypertensive Compounds Categorized by Antihypertensive Class (Continued)

Antihypertensive therapeutic class (alphabetical listing)	Foods and ingredients listed by therapeutic class	Nutrients and other supplements listed by therapeutic class
Central alpha agonists (reduce sympathetic nervous system activity)		Vitamin C
		Vitamin E
	Celery	Coenzyme Q10
	Fiber	Gamma linolenic acid
	Garlic	Potassium
	Protein	Probiotics
		Restriction of sodium
		Taurine
		Vitamin C
		Vitamin B6
		Zinc
Direct renin inhibitors		Vitamin D
Direct vasodilators	Beets (NO, ED)	Alpha linolenic acid
	Celery	Arginine
	Cocoa (NO, ED)	Calcium
	Cooking oils with monounsaturated fats	Carnitines (eNOS, NO)
	Fiber	Flavonoids
	Garlic	Grape seed extract
	Hesperidin and orange juice	Lycopene (NO, ED)
	Lycopene food (NO, ED)	Magnesium
	MUFA	Melatonin (NO, ED)
	Soy	Omega-3 fatty acids (NO, ED)
	Teas: green and black	Potassium (NO, ED)
		Taurine
		Vitamin C
Diuretics		Vitamin E
	Celery	Calcium
	Fiber	Coenzyme Q10
	Hawthorn berry	Fiber
	Protein	Gamma linolenic acid
		L-carnitine
		Magnesium
		Potassium
		Taurine
		Vitamin B6
		Vitamin C
		Vitamin E: high gamma/delta tocopherols and tocotrienols

MUFA, monounsaturated fatty acid; NAC, N-acetyl cysteine; PGD, prostoglandin; NO, nitric oxide; ED, endothelial dysfunction; eNOS endothelium-derived NO synthase.

Sodium

Increased dietary sodium intake is associated with hypertension, cerebrovascular accident (CVA), left ventricular hypertrophy (LVH), diastolic dysfunction (DD), CHD, MI, renal

insufficiency, proteinuria, arterial stiffness, platelet dysfunction, and increased sympathetic nervous system (SNS) activation. A reduction in dietary sodium intake lowers BP and the risk of all of these diseases.^{2-5,10-14,15,18,19,53-61} Decreasing dietary sodium intake in hypertensive patients, especially

salt-sensitive patients, lowers BP by 4–6/2–3 mmHg proportional to the amount of sodium restriction⁵⁴ and may prevent or delay hypertension in high-risk patients.

Salt sensitivity, defined as a $\geq 10\%$ increase in mean arterial pressure (MAP) with salt loading, increases the BP response to dietary salt intake in 51% of hypertensive patients overall, but may be even higher in African American hypertensive patients.^{57,58} Cardiovascular events may be more common in salt-sensitive patients compared to salt-resistant patients, independent of BP level.^{57,58} Decreasing sodium intake to <1500 – 2300 mg/day was associated with lower BP and a decrease in all-cause mortality, whereas increasing the intake to >2300 mg/day was associated with an increase in all-cause mortality and CVD.⁵⁶

Sodium promotes hypertension by increasing endothelial cell stiffness; reducing the size and pliability of endothelial cells; decreasing eNOS and NO production; elevating asymmetric dimethyl arginine, oxidative stress, and transforming growth factor beta; and abolishing AT2 receptor-mediated vasodilation.^{59,60,62,63} All of these effects are increased in the presence of aldosterone, which mimics these same pathophysiologic changes.^{59–61,64,65} Endothelial cells act as vascular salt sensors.^{59,60}

A balance of sodium with potassium and magnesium improves BP control and lowers cardiovascular and cerebrovascular events.^{2,65–69} Increasing the sodium/potassium ratio increases BP and the risk of CVD, but increasing the potassium/sodium ratio lowers BP and CVD risk.^{66–69} A potassium/sodium ratio of 4:1 is recommended, with a daily dietary sodium intake of 1500 mg and a dietary potassium intake of 6000 mg.^{2,66–69}

Potassium

Increased dietary potassium intake reduces BP and CVD.^{66–73} The minimal recommended intake of potassium is 4700 mg/day (120 mmol), with a potassium/sodium ratio of 4–5:1.^{66–73} Potassium supplementation at 60 mmol/day of potassium chloride for 12 weeks significantly reduced systolic BP (SBP; 5.0 mmHg in 150 Chinese subjects).⁷⁰ Prospective studies in a meta-analysis found that an intake of ≥ 1.64 g/day of potassium resulted in a 21% lower risk of stroke ($P = 0.0007$) and a lower risk of CHD and total CVD. In another meta-analysis, potassium supplementation resulted in modest but significant reductions in both SBP (4.25 mmHg) and diastolic BP (DBP; 2.53 mmHg).⁷² Studies indicate a dose-related reduction in BP of 4.4/2.5–8/4.1 mmHg with potassium supplementation, with doses between 60 and 120 mmol/day.^{2–14,66–73} Increased dietary potassium reduces CHD, MI, CHF, LVH, diabetes mellitus (DM) and cardiac arrhythmias independent of BP reduction.⁷⁰ The incidence of CVA is reduced proportional to BP reduction, but also is independent of the BP reduction.^{2–14,66–73} Chronic serum levels of potassium <4.0 meq/dL increase CVD mortality while raising the risk of ventricular tachycardia, ventricular fibrillation, and CHF.^{2–14,66–73} Red blood cell potassium is a better indication of total body stores than serum potassium.^{2–14} Increasing potassium lowers NADPH oxidase, which reduces oxidative stress and inflammation.^{2–14,66–73}

For each 1000 mg increase in daily dietary potassium, all-cause mortality is reduced by 20%, and for each 1000 mg decrease of daily dietary sodium intake, all-cause mortality is decreased by 20%.⁶⁶ The recommended daily dietary intake of potassium is 6 g in hypertensive patients with normal renal function, those not taking potassium retaining medications, or those with some other contraindication.^{2–14,66–73} Potassium sources include dark green leafy vegetables and fruits, nutritional supplements such as “No Salt” (KCL) substitutes, pure potassium powders, or combined potassium/magnesium powders and prescription KCL.^{2–4}

Magnesium

There is an inverse relationship between dietary magnesium intake and BP.^{67,74–78} In clinical trials, an increased dietary magnesium of 500–1000 mg/day lowers BP, but compared to dietary potassium intake, the effect on BP results is less pronounced.^{67,74–78} Significant reductions in BP of 5.6/2.8 mmHg, as documented by 24-hour ambulatory BP monitoring (ABPM) and home and office BP readings, usually take about two months.⁷⁴ A meta-analysis of trials found that magnesium supplementation of >370 mg/day reduced BP by 3.4 ± 2 mmHg/ 2.5 ± 1 mmHg.⁷⁷ A more recent meta-analysis (34 trials and 2028 participants) showed that magnesium supplementation dosed at 368 mg/day for three months reduced BP by 2.00/1.78 mmHg.⁷⁶ The combination of high potassium and magnesium combined with a low sodium intake potentiates the antihypertensive effects in both treated and untreated hypertensive subjects.^{67,74–78} Magnesium also competes with sodium and calcium on vascular smooth-muscle binding sites, simulates the effects of CCB, and increases NO levels and endothelial function.^{2,74–78}

Intracellular erythrocyte levels of magnesium are a more accurate assessment of total body stores compared to serum levels.^{2,67,78} Magnesium formulations chelated to an amino acid, especially magnesium with taurine, provides additional BP reduction.^{2,67,78} Transdermal preparations of magnesium and magnesium salt baths are also effective.^{2,67,78} A high magnesium diet or magnesium supplements must be used with caution in patients taking medications that promote magnesium retention, in those with known renal insufficiency, or those with other contraindications to high doses of magnesium intake. The daily dose of magnesium seems to be the primary determinant of BP reduction regardless of the method of administration. Prospective studies comparing these different delivery systems have not been done.^{2,67,78}

Calcium

Calcium supplementation is not recommended as an effective means to reduce BP until more studies are done on specific populations and age groups and the proper formulation and dose is identified. Calcium-containing foods are certainly safe to consume, but long-term use of calcium to improve BP has

not been well documented.^{79–82} The only exception is that calcium may reduce the risk of pre-eclampsia and its comorbidities for both mother and fetus.⁸²

Zinc

Low serum zinc levels correlate with hypertension and other cardiovascular problems.^{2,83,84} There is an inverse correlation between BP, serum zinc, and the zinc-dependent enzyme lysyl oxidase activity in hypertensive subjects.^{2,84} Zinc is transported into cardiac and vascular muscle and other tissues by metallothionein.⁸³ Genetic deficiencies of metallothionein lead to intramuscular zinc deficiencies and hypertension.⁸³ Zinc reduces oxidative stress, inflammation, and immune dysfunction and balances the renin-angiotensin-aldosterone system (RAAS) and SNS.^{1,2,57,58,83,84} Dietary zinc intake should be approximately 50 mg/day, and levels should be monitored with serum zinc levels.¹

Protein

Lower BP is associated with an increased intake of animal protein of all types and plant-based protein.^{2,6,85–115} Lean or wild-animal protein with a higher content of essential omega-3 FA and reduced saturated fat improves hypertension.^{86–89,115} Dietary protein intake 30% above the mean resulted in a 3.0/2.5 mmHg lower BP compared to a dietary protein intake 30% below the mean (81 g/day vs. 44 g/day).^{2,85} In a meta-analysis of 40 randomized controlled trials (RCTs), compared to carbohydrate, a higher dietary animal protein of any type and vegetable protein intake was associated with a reduction in mean BP of 1.2/0.6 mmHg.^{6,88}

In a randomized crossover study of 352 pre-hypertension and stage I hypertension subjects, soy protein from food (not powder) and milk protein, both at 25 g/day, significantly reduced SBP by 2.0 and 2.3 mmHg, respectively, with no change in DBP compared to a high glycemic index diet.⁸⁹ Soy protein intake of 25 g/day over three years was associated with a lower BP of 1.9/0.9 mmHg in 45,694 Chinese women.¹⁰¹ RCTs and meta-analyses of soy protein in hypertensive subjects indicate an average reduction in BP of 5.9/3.3 mmHg.^{101–103,105,106,108} The recommended daily intake of soy proteins from food is 25 g.²

Whey protein, milk peptides, fermented milk, and casein significantly lower BP in humans.^{2,6,90–95,104,110–115} Administration of 20 g/day of hydrolyzed whey protein lowered BP within six weeks by 8.0/5.5 mmHg.⁹¹ Milk peptides are rich in ACEI peptides, which lower BP by approximately 4.8/2.2 mmHg with doses of 5–60 mg/day.^{2,6,90–95,104} Powdered fermented milk containing *Lactobacillus helveticus* and active ACEI peptides, dosed at 12 g/day, significantly reduced BP by 11.2/6.5 mmHg in one month.⁹² Administration of 20 g of hydrolyzed whey protein to hypertensive subjects lowered BP by 11/7 mmHg compared to controls within one week.⁹⁵ The WHEY2Go trial¹¹⁰ was a randomized, double-blind,

three-way crossover, controlled intervention study of 42 participants who were randomly assigned to consume 56 g of whey protein, 56 g of calcium caseinate, or 54 g of maltodextrin (control)/day for eight weeks separated by a four-week washout. The 24-hour ABPM reductions in BP were 3.9/2.5 mmHg ($P = 0.05$), and peripheral and central SBP fell by 5.7 mmHg ($P = 0.007$) and 5.4 mmHg ($P = 0.012$), respectively, after whey protein consumption compared to the control groups, which did not significantly decrease BP.¹¹⁰ Whey protein improves endothelial function, stimulates opioid receptors, and improves PWV.

Marine collagen peptides (MCPs) derived from deep-sea fish have antihypertensive activity.^{96–98} Bonito protein (*Sarda orientalis*) from the tuna and mackerel family contains natural ACEI inhibitory peptides, and a dose of 1.5 g/day lowers BP by 10.2/7 mmHg.⁹⁷ Administration of MCPs in a double-blind placebo-controlled trial of 100 hypertensive diabetic subjects for three months significantly reduced DBP and MAP.⁹⁶

Sardine muscle protein (3 mg of VAL-TYR, a sardine muscle concentrated extract) lowered BP by 9.7/5.3 mmHg ($P < 0.05$) over four weeks in 29 hypertensive subjects.⁹⁹ A vegetable drink with sardine protein hydrolysates also reduced BP by 8/5 mmHg over 13 weeks.¹⁰⁰

The daily recommended intake of protein from all sources is 1.0–1.5 g/kg body weight, depending on exercise level, sex, age, hepatic and renal function, medications such as proton pump inhibitors and H2 blockers, and concomitant medical diseases.²

L-arginine

L arginine lowers BP in humans, with a low side-effect profile and levels similar to the DASH diet.^{116–128} L-arginine and endogenous methylarginines are the primary precursors used by eNOS to produce NO.^{116–122}

Intracellular arginine levels far exceed the K_m of eNOS under normal physiological conditions, but endogenous NO formation depends on extracellular arginine concentration. NO production by endothelial cells is closely coupled to cellular arginine transport mechanisms that regulate NO-dependent functions such as increasing renal vascular flow, renal perfusion, renal tubular NO bioavailability, and BP.¹²¹

Parenteral and oral L-arginine administration in hypertensive and normotensive subjects lowers BP significantly at doses of 10–12 g/day in food or as a supplement. Arginine administration lowers BP by about 6.2/6.8 mmHg in both office and 24-hour ABPM readings.^{116,117,123,125,126} Arginine administered at 4 g/day significantly lowered BP in gestational hypertension, reduced concomitant antihypertensive therapy, and improved maternal and neonatal outcomes with normal delivery time.^{123,124} The combination of arginine (1200 mg/day) and N-acetyl cysteine (600 mg b.i.d.) administered over six months to hypertensive patients with type 2 DM lowered SBP and DBP ($P < 0.05$).¹²⁵ Arginine may have a pro-oxidative effect and increase mortality in patients with advanced atherosclerosis, CHD, acute coronary

syndrome, or MI.¹²⁷ Pending more studies, arginine is best avoided in these situations. There are no data on L-citrulline in these settings.

Taurine

Taurine is a conditionally essential sulfur-based amino acid that is efficacious for the treatment of hypertension and a variety of CVDs by reducing SNS activity, plasma norepinephrine, and plasma and urinary epinephrine.^{2–5,14,129–136} In addition, taurine increases urinary sodium and water excretion, atrial natriuretic factor (ANF), and NO bioavailability; improves ED; and increases EPCs, while it decreases plasma renin activity, A-II, and plasma aldosterone.^{2–5,129–131} Nineteen hypertensive subjects administered 6 g of taurine daily lowered BP by 9/4.1 mmHg ($P < 0.05$) in seven days.¹³⁰ In a randomized, double-blind, placebo-controlled study over 12 weeks in 120 prehypertensive individuals, taurine supplementation (1.6 g/day) significantly improved endothelial function and decreased the clinic and 24-hour ABPM reading by 7.2/2.6 mmHg and 4.7/1.3 mmHg, respectively.¹³⁶ In another four-month study of 97 pre-hypertensive individuals, 1.6 g/day of taurine significantly decreased the clinic and 24-hour ABPM, improved endothelium vasodilation, and reduced the carotid IMT.¹³⁴

In a randomized, double-blind, placebo-controlled study of 42 hypertensive subjects evaluated over one month, a combination powder dietary supplement was given once daily.¹³⁵ The supplement included 6 g of taurine, 1000 mg of vitamin C (as magnesium ascorbate), 150 mg of grape seed extract, 87 mg of magnesium ascorbatet, 100 mg of vitamin B6 (pyridoxine HCl), 2000 IU of vitamin D3, and 2 mg of biotin. The active group had a reduction in BP of 16/11.35 mmHg ($P < 0.001$) at week 4. The recommended dose of taurine is 1.5–6 g/day as a single dose or in divided doses.^{2,129–136}

Omega-3 Fats and Selected Omega-6 Fats

Omega-3 FA derived from food or nutritional supplements produce a dose-related reduction in BP and CVD in published human studies.^{2–14,115,137–152} A meta-analysis of 70 RCTs found that compared to placebo, the consumption of omega-3 polyunsaturated FA (PUFAs; 0.3–15 g/day) for 4–26 weeks significantly reduced BP by 1.5/1.0 mmHg.¹⁴⁶ The largest BP reductions were in untreated hypertensive subjects (SBP = 4.5 mmHg [95% confidence interval (CI) –6.1 to –2.8 mmHg]; DBP = –3.0 mmHg [95% CI –4.3 to –1.7 mmHg]).¹⁴⁶ A second meta-analysis of RCTs found that omega-3 FA supplementation for 6–105 weeks at 900–3000 mg/day improved PWV ($P < 0.01$) and arterial compliance ($P < 0.001$).¹⁴⁷ Docosahexaenoic acid (DHA) is more effective than eicosapentaenoic acid (EPA) in reducing BP by an average of 8/5 mmHg and also lowering the resting heart rate by 6 bpm and improving heart rate variability.^{2–14,137–139,142–144}

Administration of EPA and DHA is preferred to alpha linolenic acid due to the latter's minimal conversion to these longer-chain omega-3 FA.^{2–14,138,140} The consumption of cold-water fish three times per week reduces BP due to the combination of protein and omega-3 FA.^{2–14,109,138} In patients with chronic kidney disease, 4 g of omega-3 FA significantly lowered 24-hour BP (ABPM) by 3.3/2.9 mmHg compared to placebo ($P < 0.0001$).¹³⁹ Omega-6 FA, gamma-linolenic acid (GLA), and dihomo-gamma linolenic acid reduce BP and prevent elevations in BP induced by saturated fats.¹⁴³ GLA blocks stress-induced hypertension, lowers aldosterone levels, decreases adrenal AT1R density and affinity, and increases the vasodilating prostaglandins E1 (PGE1) and PGI2.^{2–14,143}

Omega-3 FA reduce CHD and MI¹⁵²; increase eNOS and NO; improve endothelial function; reduce arterial stiffness; decrease PWV, insulin resistance, and plasma norepinephrine; suppress ACE activity; and increase parasympathetic tone at doses of 900–3000 mg/day.^{2–14,137,145,148} The recommended daily dose is 3000–5000 mg/day of combined DHA and EPA at a ratio of three parts EPA to two parts DHA, with 50% of this dose as GLA combined with gamma plus delta tocopherols at 100 mg/g of DHA and EPA to get the red blood cell membrane omega-3 index at 8%.^{2–5} There are no adverse effects or safety concerns at these recommended doses.^{2–14}

Monounsaturated FA: Olive Oil, MedDiet, Omega-9 Fats, Oleic Acid, and Olive Leaf Extract

The MedDiet, which is rich in olive oil and olive leaf extracts (OLE), reduces BP and CVD in most clinical trials.^{2–14,153–176} In an open study over two months, 40 borderline hypertensive monozygotic twins given either 500 or 1000 mg/day of OLE had significant reductions in BP of 6/5 mmHg (500 mg of OLE) and 13/5 mmHg (1000 of OLE) compared to controls.¹⁷⁶ In another randomized, double-blind placebo-controlled trial, the BP decreased by 8/6 mmHg ($P \leq 0.01$) in office and 24-hour ABPM, and the need for antihypertensive medications reduced by 48% in the monounsaturated fatty acid (MUFA) group ($P < 0.005$).¹⁵³ Extra virgin olive oil (EVOO) lowered the SBP by 14 mmHg in elderly hypertensive patients ($P < 0.01$).^{154,155} EVOO contains lipid-soluble phytonutrients such as nitrates and polyphenols, which lower BP by reducing oxidative stress and oxLDL, blocking the AT1R, altering RAAS and endothelin gene expression, increasing NO levels and endothelial induced vasodilation, and blocking calcium channels similar to a CCB.^{150,153,157,164–166} EVOO with a total phenol content of at least 161 mg/kg at 20–40 g (2–4 tbsp) per day will significantly lower SBP in about three weeks. EVOO with 300 mg/kg of total phenols may also decrease DBP.^{2–5,170}

A total of 166 elderly subjects were prescribed a MedDiet or their habitual diet (HabDiet; control) for six months.¹⁷⁴ Compared to the HabDiet, the MedDiet lowered SBP by

1.1 mmHg and improved flow-mediated vasodilation at six months ($P = 0.01$). The INTERMAP trial found that dietary MUFA intake, especially oleic acid from vegetable sources, may contribute to the prevention and control of adverse BP levels in the general population.¹⁷⁵

In the European Prospective Investigation into Cancer and Nutrition (EPIC) study (20,343 subjects), the intake of EVOO and polyphenols documented an inverse relationship with SBP and DBP.¹⁷¹ In the Prevention with Mediterranean Diet (PREDIMED) trial that included 7447 patients at high risk for CVD, the participants on the MedDiet supplemented with EVOO had a significantly lower DBP than those in the control group (1.5 mmHg).¹⁷²

OLE is associated with a dose-dependent reduction in BP, with a range of 4/3–11/5 mmHg with both office BP measurements and 24-hour ABPM.^{167–169,173} A total of 60 pre-hypertensive male subjects in a six-week study with OLE demonstrated a reduction in BP of about 4/3 mmHg.¹⁶⁷ Olive (*Olea europaea*) leaf extract, at the dosage regimen of 500 mg b.i.d., was similarly effective in lowering SBP and DBP in subjects with stage 1 hypertension compared to captopril, given at its effective dose of 12.5–25 mg b.i.d. (reduction of about 11/5 mmHg).¹⁶⁹

Vitamin C

Dietary intake of vitamin C and plasma ascorbate concentration in humans are inversely correlated to BP.^{2–14,177–199} The administration of vitamin C orally and intravenously reduced BP in clinical trials.^{2–14,177–199} Thirty-one patients were randomized to 500, 1000, or 2000 mg of oral vitamin C daily, with a mean reduction in BP of 4.5/2.8 mmHg ($P < 0.05$).¹⁹⁴ There was no difference between the three vitamin C groups, indicating that 500 mg daily or 250 mg b.i.d. is sufficient to reduce BP.¹⁹⁴ In a meta-analysis of 29 trials with a median dose of vitamin C of 500 mg/day and a median duration of two months, there was a significant reduction in BP of 3.84/1.48 mmHg ($P = 0.04$).¹⁹⁹ Published clinical trials show that vitamin C at a dose of 250 mg b.i.d. reduces BP by an average of 7/4 mmHg.^{2–14,177–199} Vitamin C is a potent water-soluble antioxidant and electron donor that recycles vitamin E and other antioxidants and enhances total antioxidant capacity.¹⁷⁷ In elderly patients with refractory hypertension already on maximum pharmacologic therapy, 600 mg of vitamin C daily lowered BP by an additional 20/16 mmHg.¹⁸⁶ Plasma ascorbate is inversely correlated with BP in healthy, normotensive individuals, and those with the lowest initial ascorbate serum levels have the best BP reduction.^{2–5,187,193} SBP and the 24-hour ABPM show the most significant reductions with chronic oral administration of vitamin C.^{2,181–186} In a depletion-repletion study of vitamin C, Block et al.¹⁸⁷ demonstrated an inverse correlation of plasma ascorbate levels, SBP, and DBP. In a meta-analysis of 13 clinical trials with 284 patients, vitamin C at 500 mg/day over six weeks reduced BP by 3.9/2.1 mmHg.¹⁸⁸ Hypertensive subjects have significantly lower plasma ascorbate levels compared to normotensive subjects

(40 μ mol/L vs. 57 μ mol/L, respectively).^{190,199} A serum level of 100 μ mol/L is recommended for optimal BP lowering.^{2–5}

Vitamin E

Very few clinical studies have demonstrated improved BP with supplementation with the various types of tocopherols or tocotrienols.^{2,200–204} Patients with type 2 DM on prescription medications with controlled BP (average BP of 136/76 mmHg) were administered 400 mg of mixed tocopherols containing 60% gamma, 25% delta, and 15% alpha tocopherols.²⁰⁰ The BP increased by 6.8/3.6 mmHg in the study patients on the mixed tocopherols ($P < 0.0001$) and increased even more in those subjects taking alpha tocopherol (BP increased by 7/5.3 mmHg; $P < 0.0001$).²⁰⁰ The BP increase was likely due to drug interactions with tocopherols via cytochrome P450-3A4 and 4F2 that decreased the effective serum levels of the anti-hypertensive medications.²⁰⁰ Gamma tocopherol has an anti-hypertensive and natriuretic effect through the inhibition of the 70pS potassium channel in the thick ascending limb of the loop of Henle.²⁰¹ Both alpha and gamma tocopherol improve insulin sensitivity and enhance adiponectin expression via a PPAR- γ -dependent process, which has the potential to lower BP and serum glucose.²⁰²

In a retrospective analysis and data from the National Health and Nutrition Survey, the medium and high tertiles of vitamin E intake were associated with a significantly lower odds ratio for hypertension (0.73 and 0.81, respectively).²⁰³ In a randomized, double-blind, placebo-controlled trial of 58 individuals with type 2 DM, 500 mg/day of RRR- α -tocopherol, 500 mg/day of mixed tocopherols, or placebo for six weeks did not significantly alter the rate of daytime or night-time SBP, DBP, or pulse pressure variation compared to placebo ($P > 0.05$).²⁰⁴ If vitamin E has an antihypertensive effect, it is probably small and may be limited to patients with untreated hypertension, vitamin E deficiency, known vascular disease, mild volume overload, or other concomitant problems such as DM or hyperlipidemia.^{2–5,200–204}

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