The Role of Vascular Biology, Nutrition and Nutraceuticals in the Prevention and Treatment of Hypertension

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ABSTRACT

Vascular biology plays a primary and pivotal role in the initiation and perpetuation of hypertension and subsequent target organ damage. Endothelial activation and dysfunction, oxidative stress and vascular smooth muscle dysfunction (hypertrophy, hyperplasia, remodeling) may be some of the first events that trigger essential hypertension. Nutrient-gene interactions determine specific phenotypic consequences of either vascular health, vascular disease or hypertension. Optimal nutrition, nutraceutical supplements, vitamins, antioxidants, minerals, weight loss, exercise, smoking cessation and judicious restriction of alcohol and caffeine as well as other lifestyle modifications can prevent, delay the onset, reduce the severity, treat and control the essential hypertension of many patients. An integrative and synergistic approach combining these lifestyle modifications with appropriate pharmacologic treatment is most likely to achieve new goal blood pressure levels, reduce risk factors for vascular disease, improve vascular biology and vascular health, optimize target organ protection and reduce coronary heart disease, stroke, congestive heart failure and renal disease. This paper will review the expanded scientific roles for nutrition and nutraceutical supplements in the prevention and treatment of essential hypertension with specific emphasis on mechanisms of action, clinical use and integration with drug therapy as indicated, based in part on the Joint National Committee’s 6th Report (JNC-VI) and other national and global hypertension guidelines.

INTRODUCTION

Hypertension is a consequence of the interaction between genetics and the internal environment of the body. Macronutrients and micronutrients are crucial in the regulation of blood pressure (BP) and subsequent target organ damage (TOD). Nutrient-gene interactions, oxidative...
stress and subsequent gene expression have positive or negative influences on vascular biology in humans. Endothelial dysfunction and vascular smooth muscle dysfunction are the initiating and perpetuating factors in essential hypertension. The correct combination of macronutrients and micronutrients significantly influences the prevention and treatment of hypertension and its vascular complications. Our genes determine who we are, how we look and even how we think. However, our lifestyle and nutritional choices will influence our physical and mental health and ultimately our fate.1

Nutritional needs have changed as we have evolved from a pre-agricultural, hunter-gatherer milieu to a highly technological agricultural industry dependent on mechanical processing for our food supply.1,2 Movement from the Paleolithic diet with low sodium, high potassium, high fiber, low fat, lean animal protein, low refined carbohydrate, and low cholesterol intake composed of fruits, vegetables, berries, nuts, fiber, fish, fowl, and wild game to our modern diet has resulted in an epidemic of nutritionally-related diseases. These diseases include hypertension, atherosclerosis and target organ diseases (TOD) such as coronary heart disease (CHD), congestive heart failure (CHF), cerebrovascular accidents (CVA), myocardial infarction (MI), renal insufficiency (RI), and renal failure (RF).2

Short-term reduction in blood pressure (BP) by nutritional means translates into intermediate and long-term improvements in morbidity and mortality, including CVA, CHD and MI.3,4 In the Health Professionals Followup Study,3 diets rich in potassium reduced CVA by 41% in hypertensive subjects. In the Lyon Diet Heart Study,4 a Mediterranean-type diet reduced the incidence of a second MI by 76%. These and other studies to be addressed testify to the importance of micronutrients, macronutrients and specific nutraceuticals in the prevention and treatment of hypertension and its cardiovascular sequelae. Many national and global organizations (such as the JNC-VI,5 the Nutrition Committee of the American Heart Association,6 the World Health Organization (WHO) and the Institute of Medicine) report to Congress7 on the nutritional needs of the elderly, INTERSALT8 and numerous others recognize the impact of nutrition in hypertension, CHD, atherosclerosis, CVA and overall disease prevention.7,8,9

NUTRITION AND DISEASE PREVENTION

A wise healer uses that which works. An integrative and synergistic approach that embraces nutrition, nutraceuticals, weight loss, exercise, judicious limited use of alcohol, and tobacco cessation with appropriate pharmacologic therapy (antihypertensive drugs) is clearly the optimal means to lower BP and reduce TOD in specific subsets of essential hypertensive patients. Lower BP goals in essential hypertensive patients will make combining lifestyle modifications and drug therapy a requirement for many patients, including those with multiple risk factors, TOD or clinical cardiovascular disease (CCD). These include hypertensive patients with diabetes mellitus, renal insufficiency (RI), proteinuria or microalbuminuria, those with present or previous TOD (cerebrovascular accident [CVA], coronary artery bypass graft [CABG], left ventricular hypertrophy [LVH], transient ischemic attack [TIA], nephropathy, peripheral arterial disease, retinopathy) and those with concomitant CHD risk factors such as dyslipidemia, homocysteinemia, insulin resistance, hyperglycemia, diabetes mellitus, tobacco use, being elderly, being male, being a postmenopausal woman, or having a family history of premature cardiovascular disease (women < 65, men < 55) (Table 1 and Table 2).

These lifestyle modifications may prevent, delay the onset, reduce BP levels and its progression, potentiate the effects of antihypertensive drugs (which allow for fewer drugs and/or lower doses) and provide additive or synergistic improvements in risk factors, BP and vascular function, structure and health.10,11 Patients with high normal BP (BP 130-139/85-89 mm Hg) or Stage 1 hypertension (BP 140-159/90-99 mm Hg) who have no risk factors, TOD or clinical cardiovascular disease (CCD) (Risk Group A), should be treated with lifestyle modification for up to 12 months5 (Table 1 and Table 2). These same patients in Risk Group B with only one risk factor (excluding diabetes) and no TOD or CCD should be treated with lifestyle modification for up to six months.5 If the BP remains elevated beyond six months, then antihypertensive drug therapy should be initiated (Table 1 and Table 2).

However, a large percentage of essential hypertensive patients are appropriate candidates for initial and prolonged lifestyle modifications as long as the BP is frequently evaluated and clinical TOD, CCD or significant risk factors are not present at that time and do not develop later. As many as 50 to 60% of essential hypertensive patients may fall into this classification.11,12,13 Nutrition, nutraceutical supplements, weight loss, exercise, cessation of tobacco use, and judicious limited use of alcohol are effective therapy in these patients and provide excellent adjunctive therapy in patients on antihypertensive drugs. The lifestyle modifications mentioned above should always be continued following initiation of drug therapy.10,11,12,13

This paper will review the basic science and clinical studies of nutrition, nutraceutical supplements, vitamins, antioxidants, minerals, macronutrients, micronutrients, exercise, weight loss, weight management, and alcohol and caffeine consumption and their role in the prevention and treatment of hypertension. Correlations and mechanisms of action based on vascular biology will provide a unique framework for understanding the clinical use of these lifestyle modifications. A review of pharmacologic therapy with antihypertensive drugs is beyond the scope of this paper, but some general discussion is provided to emphasize the importance of “balance” when treating essential
hypertension. Extreme opinions about lifestyle modifications or treatments with alternative non-drug therapy versus drug therapy serve little purpose except to polarize ideas and health care providers at the expense of their patients’ welfare. Therapeutic choices must be based on good science, not on whims, misconceptions and ignorance. It is time to integrate nutrition and nutraceutical science with traditional drug therapy to reduce BP, TOD and improve the dismal BP control in the U.S. and other countries.5,14,15,16,17

Indeed, the wise healer will use what works, is safe and based in good science. Our goal is to improve our patients health and quality of life. Let fruitful scientific and rational discussions begin and the rhetoric end. A belief that certain treatments are true or untrue, or thinking that it is counter-intuitive or unproven can no longer be considered acceptable medical practice. The truth awaits to be revealed.

“The doctor of the future will give no medicine, but will interest his patient in the care of the human frame, in diet and in the cause and prevention of disease” - Thomas Edison.

**Epidemiology of Hypertension**

Approximately 25% of the United States adult population (over 50 million people) have hypertension as defined by a BP reading over 140/90 mm Hg.5,14,15,18 This percentage increases with age, such that 50% of adults over age 60, and 80% of adults over age 70 have hypertension.5,14,15,18 Although 90 to 95% of hypertension is genetic, environment (nutrition and exercise) influences its age of onset and severity.5,14 In general, African Americans, men and the elderly have more severe hypertension and increased target organ damage (TOD) at similar BP levels compared to Caucasians, women and younger patients.5,14,15,18 However, after age 60, women have a greater incidence of hypertension than men.5,14 About 70% of patients with essential hypertension have BP < 160/105 mm Hg.10

Hypertension is the leading cause of cardiovascular and cerebrovascular complications, the most common reason for visits to physician offices, and the number one reason for drug prescriptions in the U.S.5,14,19,20 The annual expenditure for antihypertensive drug prescriptions is over 10 billion dollars,14 an amount projected to exceed 25 billion dollars by 2007. The National Health and Nutritional Examination Survey III (NHANES III) found that only 27% of the hypertension population had controlled their blood pressure to a goal of less than 140/90 mm Hg.5,14,15,17 This percentage is less than in 1990, yet the expenditure on antihypertensive medications has doubled.5,14,15,17

Cardiovascular and cerebrovascular disease increase dramatically with small increases in BP, even while remaining within normal range.5,21 In fact, 32% of CHD deaths secondary to hypertension occur with a systolic blood pressure (SBP) of less than 140 mm Hg.22 Reducing BP results in impressive decreases in CHD, MI, CHF, CVA and RI.5,18,23,24 A reduction in diastolic blood pressure (DBP) of 5 mm Hg reduces CHD by 15%, CHF by 52% and CVA by 40%.5,18,23 A 3 mm Hg reduction in SBP reduces CHD by 5% and CVA by 8%.18,24 Even with adequate BP control on antihypertensive medications, hypertensive patients still have a substantially and significantly 30% higher risk of cardiovascular morbidity and mortality compared to untreated, normotensive patients.25 The reasons for this are not established, but a negative influence of diuretics and beta blockers on CHD risk factors, the presence of the hypertension syndrome and its constellation of risk factors or abnormalities of vascular biology may be important contributing factors.25

### Classification of Hypertension

The Joint National Committee’s 6th Report has classified BP into four major groups (Table 1).5 Hypertension is stratified into Stage 1, 2 and 3 based on either systolic (SBP), or diastolic blood pressure (DBP) (Table 1).5 Treatment is determined by BP level, risk factors, TOD, CCD or presence of diabetes mellitus (DM) (Table 2).5 It should be emphasized that lifestyle modification or non-pharmacologic therapy is recommended for up to 12

### Table 1

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic BP (mmHg)</th>
<th>Diastolic BP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Optimal</strong></td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td><strong>Normal</strong></td>
<td>&lt;130</td>
<td>&lt;85</td>
</tr>
<tr>
<td><strong>High-normal</strong></td>
<td>130-139</td>
<td>85-89</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stage 1</strong></td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td><strong>Stage 2</strong></td>
<td>160-179</td>
<td>100-109</td>
</tr>
<tr>
<td><strong>Stage 3</strong></td>
<td>≥180</td>
<td>≥110</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Risk Stratification and Treatment†</th>
<th>Risk Group A</th>
<th>Risk Group B</th>
<th>Risk Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BP stage</strong></td>
<td>No risk factors</td>
<td>At least one risk factor, not including diabetes</td>
<td>No TOD / CCB†</td>
</tr>
<tr>
<td><strong>SBP (mmHg)</strong></td>
<td><strong>DBP (mmHg)</strong></td>
<td><strong>SBP (mmHg)</strong></td>
<td><strong>DBP (mmHg)</strong></td>
</tr>
<tr>
<td>High-normal</td>
<td>Lifestyle modification</td>
<td>Lifestyle modification</td>
<td>Drug Therapy†</td>
</tr>
<tr>
<td>(140-159 / 90-99)</td>
<td>(≥160 / ≥100)</td>
<td>(≥160 / ≥100)</td>
<td>(≥160 / ≥100)</td>
</tr>
<tr>
<td>Stage 1</td>
<td>Lifestyle modification</td>
<td>Lifestyle modification</td>
<td>Drug Therapy†</td>
</tr>
<tr>
<td>(140-159 / 90-99)</td>
<td>(≥160 / ≥100)</td>
<td>(≥160 / ≥100)</td>
<td>(≥160 / ≥100)</td>
</tr>
<tr>
<td>Stage 2 and 3</td>
<td>Drug Therapy†</td>
<td>Drug Therapy†</td>
<td>Drug Therapy†</td>
</tr>
</tbody>
</table>

†Sodium modification should be adjunctive therapy for all patients, in addition to prescribed therapy for hypertension.

‡For patients with diabetes or chronic kidney disease or chronic obstructive pulmonary disease.

§For patients with heart failure or renal insufficiency or those with diabetes.
months in patients with Stage 1 hypertension in Risk Group A and up to six months in Risk Group B. These patients have BP ≤ 160/100 mm Hg without DM, TOD, or CCD, but may have one CV risk factor (Group B). Group C patients with TOD, CCD, DM, or more than one CV risk factor should immediately receive drug therapy. Nonpharmacologic therapy should be adjunctive treatment for all patients on pharmacologic therapy regardless of Stage or Risk Group. Patients with Stage 2 and 3 hypertension should initially receive antihypertensive drug therapy (BP > 160/100 mm Hg) regardless of Risk Group category, and continue on lifestyle modifications as well.

The primary TOD in hypertension includes CHD, MI, CHF (both systolic CHF and diastolic CHF), CVA, RI or RF, large arterial disease (aorta and peripheral vascular disease) and retinopathy. Goal BP levels should be approximately 110/70 mm Hg in patients with DM, chronic renal insufficiency (CRI), proteinuria, CHD or a history of CVA.

**RISK FACTORS AND HYPERTENSION**

The most common and important risk factor for the development of hypertension is genetics. A positive family history in a parent results in a 25 to 50% chance of a child developing the polygenic and multifactorial disorder called hypertension. Other risk factors include unhealthy nutrition, obesity, alcohol, high sodium intake, chronic and acute stress, increased unrefined carbohydrate and sugar intake, sedentary lifestyle, age, ethnicity, gender, tobacco use and possibly caffeine intake. Oxidative stress has assumed a major role in the initiation and perpetuation of hypertension.

Numerous studies have shown that appropriate nutrition, macronutrients, micronutrients and other lifestyle changes can prevent or significantly reduce the incidence of hypertension in any age group, gender or race. In the Trials of Hypertension Prevention Phase 2 (TOHP-2), sodium restriction, weight loss, or a combination reduced the incidence of hypertension at year four by 18-22% compared to the control group of a middle-aged, obese, nonhypertensive population. The incidence of hypertension in the control group was 7.3% versus 4.5% in the sodium restricted group, 4.2% in the weight reduction group, and 2.7% in the group with combined sodium restriction and weight loss. Sodium restriction in normotensive newborns of hypertensive parents administered for six months resulted in a reduced BP and prevented BP elevation that was maintained for fifteen years. Elderly patients with hypertension are quite sensitive to sodium restriction. In the Trial of Nonpharmacologic Interventions in the Elderly (TONE), a 40 mmol/day reduction of sodium decreased the need for hypertensive medications in 40% of subjects at three months. In addition, a weight loss of 10 pounds reduced the need for medication by 36%, and the combination of sodium restriction and weight loss reduced the need for medication by 53% in those subjects with an initial BP ≤ 145/85 mm Hg. African American hypertensive patients tend to have a greater reduction in BP than Caucasians with the same dietary interventions.

**HYPERTENSION SYNDROME**

Hypertension is associated with a constellation of clinical, metabolic, biochemical and structural abnormalities in over 70% of cases. These abnormalities may actually precede the development and/or diagnosis of hypertension by many years. The hypertension syndrome consists of endothelial dysfunction, reduced arterial and ventricular compliance, abnormal glucose metabolism and insulin resistance, endocrine and neurohormonal dysfunction, renal function changes, clotting changes with a thrombotic tendency, left ventricular hypertrophy (LVH), diastolic dysfunction, accelerated atherogenesis, abnormal lipid metabolism and central obesity. Hypertension is a disease of the blood vessel in which the vascular biology is altered and dysfunctional.

It appears that many of the changes in vascular structure and function antedate the onset of hypertension by decades and may be responsible for its ultimate development. Identification of the syndrome, followed by aggressive, appropriate nutrition, exercise, weight management and nutraceutical treatment of these patients before hypertension becomes chronically established will improve and even reverse cardiovascular disease.

Dyslipidemia and hypertension are genetically inherited and genetically linked, but are variables that occur independently of each other. Approximately 80% of hypertensive patients have concomitant dyslipidemia. Dyslipidemia in patients with a positive family history of hypertension is significantly more frequent than in those without a family history of hypertension despite being normotensive.

Left ventricular hypertrophy (LVH) precedes the development of hypertension in young, normotensive adults who have a positive family history of hypertension and is significantly more common compared to age-matched normotensive controls without a family history of hypertension. Thus, LVH, although commonly associated with hypertension in over 50% of patients, is also genetically determined, may be independent of and precede the onset of hypertension. Similarly, diastolic dysfunction or reduced ventricular compliance precedes hypertension and is more common in normotensive patients with a positive family history of hypertension compared to normotensive controls with a negative family history of hypertension.

Reductions in arterial compliance with increased arterial stiffness occur before the onset of hypertension, follow a similar family history, may not worsen with increasing BP, but it is associated with the pathophysiology of
elevated BP and is a marker for an increased incidence of adverse cardiovascular outcomes.39,40

Insulin resistance occurs in 50% of untreated hypertensive patients.39,40,41 The resulting hyperinsulinaemia may cause endothelial dysfunction (ED), hypertension, dyslipidemia, central obesity, hypercoagulable state, VSM hypertrophy, atherosclerosis, sodium retention, increased SNS activity and glucose intolerance or DM, which may be exacerbated by diuretics and beta blockers.39,40,41 Insulin resistance and all of its consequences can be treated and reversed with the implementation of a low fat (reduced saturated and trans fats with more polyunsaturated omega-3 fatty acids and monounsaturated fats), unrefined-carbohydrate diet without caloric restriction.41

Abnormalities in renal function have been demonstrated in children of parents with hypertension compared to children of normotensive parents.39,40 These include the inability to increase creatinine clearance after a protein load, more microalbuminuria and hyperuricemia.39,40 These renal changes precede the onset of hypertension.

Neuroendocrine changes such as significantly elevated plasma renin activity (PRA) and plasma norepinephrine (NE) levels occur in normotensive children with hypertensive parents more often than normotensive children without a family history of hypertension, and these neuroendocrine changes precede the development of hypertension.39,40

It is apparent that normotensive children or adults with a family history of hypertension have a cardiovascular risk profile that is similar to hypertensive patients. This has led to the term “normotensive hypertension” to indicate that these subjects have not yet developed hypertension, which may be a late cardiovascular marker of vascular damage, but they are at risk to develop significant cardiovascular disease. The therapeutic implications of the hypertension syndrome are enormous. Early detection, aggressive lifestyle modifications including optimal nutrition, exercise, weight management, nutraceuticals, risk factor control and other daily lifestyle changes are mandatory to prevent cardiovascular disease and hypertension.

Hypertension is not just a simple disease consisting of elevated blood pressure, but is part of a complex syndrome. It is imperative that a new approach to prevention and treatment of hypertension be directed at treating the blood vessel, to optimize control of these abnormalities to maximally decrease TOD (Figure 1).

**ARTERIOSCLEROSIS AND ATHEROSCLEROSIS**

Although there are clear differences in arteriosclerosis and atherosclerosis, recent research in vascular biology indicates similar mechanisms that adversely effect the blood vessel and result in both processes. There is much overlap in pathogenesis, as well as in functional and structural outcomes (Table 3).43 Treatment directed at endothelial dysfunction, vascular smooth muscle dysfunction and abnormal arterial compliance may slow or halt progression to arteriosclerosis and atherosclerosis.

**ENDOTHELIAL DYSFUNCTION, OXIDATIVE STRESS, ATHEROSCLEROSIS, CARDIOVASCULAR RISK FACTORS AND CORONARY HEART DISEASE**

Many traditional, nontraditional, and emerging cardio-

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**Table 3**

<table>
<thead>
<tr>
<th>Arteriosclerosis and Atherosclerosis</th>
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</thead>
<tbody>
<tr>
<td><strong>Arteriosclerosis</strong></td>
</tr>
<tr>
<td>(increased vascular stiffness, decreased vascular compliance)</td>
</tr>
<tr>
<td><strong>Atherosclerosis</strong></td>
</tr>
<tr>
<td>Focal, occlusive</td>
</tr>
<tr>
<td>Inflammatory</td>
</tr>
<tr>
<td>Endothelial dysfunction</td>
</tr>
<tr>
<td>Related to LDL cholesterol oxidation</td>
</tr>
<tr>
<td>“Inside-out”</td>
</tr>
<tr>
<td>Sensitive to angiotensin-II and other substances</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Diffuse, dilatory</strong></td>
</tr>
<tr>
<td><strong>Fibroate (collagen replaced by collagen)</strong></td>
</tr>
<tr>
<td><strong>Adventitial and medial hypertrophy</strong></td>
</tr>
<tr>
<td><strong>Related to age and blood pressure</strong></td>
</tr>
<tr>
<td><strong>“Outside-in”</strong></td>
</tr>
<tr>
<td><strong>Sensitive to angiotensin-II and other substances</strong></td>
</tr>
</tbody>
</table>

*Data, Arch Intern Med 1994, 154: 917-920*
vascular risk factors can directly cause oxidative stress or endothelial dysfunction (ED) and vascular dysfunction leading to atherosclerosis, arteriosclerosis and TOD (Figure 2). Oxidative stress may induce hypertension and oxidize LDL cholesterol resulting in further ED, atherosclerosis and TOD. This cycle becomes self-perpetuating with progressive vascular damage and high cardiovascular morbidity and mortality.

THE BLOOD VESSEL

The blood vessel becomes the primary and central organ in the pathogenesis of cardiovascular disease and hypertension. The blood vessel structure is shown in Figure 3 and consists of the intima (endothelium and connective tissue), the media (vascular smooth muscle, a protein matrix of elastin and collagen, and an internal elastic lamina), and the adventitia with strong fibrous tissue to maintain vessel shape.44,45

The vascular endothelium is the largest endocrine organ and the largest organ in the body.46 It is 14,000 ft² in surface area, the size of 6 1/2 tennis courts in square area, and 5 times the heart size in mass with a total weight of about 2 kilograms.46,47,48,49,50,51 It is a metabolically active organ with endocrine, paracrine, autocrine and intracrine functions.

The vascular endothelium under normal, healthy physiological conditions forms a continuous sheet of organized monolayer polyhedral cells that becomes disorganized at extremes of hemodynamic shear stress (hypotension and hypertension).46,47,48,49,50,51

Endothelial cells create a conduit that regulates blood flow through the tissues. Small vessels and capillaries consist primarily of endothelial cells, while larger vessels have additional components including connective tissue and smooth muscle that add strength and tone to the vessel.46,47,48,49,50,51

The endothelium, which forms a barrier between the blood and the tissues, is a living organ with multiple functions. The endothelial cells are tightly interlocked so that passage of products from the blood occurs through the endothelial cell. These cells are both a passive filter and a metabolically active organ that secretes substances into and out of the blood and into the underlying vascular smooth muscle, which regulates the local milieu.46,47,48,49,50,51

ENDOTHELIAL FUNCTION

The strategic location of the endothelium allows specific modulation of elements in the blood and vascular smooth muscle cell (Figure 4).49,51 Modulation in the circulating blood controls platelet function, coagulation, monocyte and leukocyte adhesion and inflammation. Modulation of the vascular smooth muscle cells (VSMC) determines permeability, contractile state, proliferative or growth response, migratory response and redox state. The endothelium maintains vascular health by a carefully controlled balance of...
“good” or “bad” mediators (Figure 5). Mediators that are involved in vascular tone and redox state are listed in Tables 4 and 5 respectively.

Endothelial activation and subsequent responses are shown in Figure 6. Activation of endothelial receptors can stimulate nitric oxide (NO) synthase (NOS) with the production of NO and cyclooxygenase (COX), which produces prostacyclin [PGL_2] from arachidonic acid [AA] and can lead to the release of endothelium-derived hyperpolarizing factor (EDHF). NO causes relaxation by activating the formation of cyclic GMP (cGMP) from guanosine triphosphate (GTP) by soluble guanylate cyclase (SGC). Prostacyclin (PGL_2) causes relaxation by activating adenylate cyclase (AC) leading to the formation of cyclic AMP (cAMP). EDHF produces hyperpolarization and relaxation by opening K^+ channels. Any increase in cytosolic calcium causes the release of relaxing factors. In certain blood vessels, contracting substances can be released from the endothelial cells, which include superoxide anions (O_2^-), thromboxane A_2 (TXA_2), endoperoxides and possibly endothelin-1 (ET-1). Thromboxane A_2 and endoperoxides activate specific receptors (TX/Endo) on the vascular smooth muscle, as does ET_1. Such activation causes an increase in intracellular Ca^{2+} leading to contraction. The production of ET-1 (catalyzed by endothelin converting enzyme [ECE]) can be augmented by angiotensin II (ATII), vasopressin (VP) or thrombin (T). The neurohumoral mediators, which induce the release of endothelium-derived relaxing factors (and sometimes contracting factors) through activation of specific endothelial receptors include: acetylcholine (ACh); adenosine diphosphate (ADP); bradykinin (BK); endothelin (ET); adrenaline (A); serotonin (5HT); thrombin (T); vasopressin (VP).

NITRIC OXIDE: CARDIOVASCULAR EFFECTS

Nitric oxide is the most powerful endogenous vasodilator. It maintains basal vascular tone, but is also produced and released both tonically and under stimulation. It inhibits the atherosclerotic process and lowers blood pressure. Nitric Oxide is synthesized in the endothelium and vascular smooth muscle by nitric oxide synthase with a very short half-life of only a few seconds. Nitric Oxide is involved in numerous biologic functions but only its cardiovascular effects which include vasodila-
tion, anti-atherosclerotic, anti-platelet, anti-growth and anti-oxidant effects, will be considered here (Table 6). The results of NO inhibition are shown in Figure 7.

ENDOTHELIAL DYSFUNCTION

Endothelial dysfunction occurs when the vascular endothelium undergoes a phenotypic modulation to a non-adaptive state characterized by the loss or dysregulation of critical homeostatic mechanisms that normally operate in healthy endothelial cells. The endothelial cell, VSMC and emigrated leukocytes (EML) are all oxidant stress sensors and the source of the biologic modification response.

The two major paradigms of endothelial activation are biochemical and biomechanical (Figure 8). Activation results in release of numerous mediators with endocrine, paracrine, autocrine and intracrine actions. Endothelial activation and dysfunction is the key, initial event in vascular disease, present with only risk factors, but no atherosclerosis. Endothelial dysfunction precedes intimal thickening by a decade and clinical atherosclerosis by several decades. Endothelial dysfunction has a high correlation with future cardiovascular events such as MI, percutaneous transluminal angioplasty, coronary artery bypass graft and sudden death. Hypertensive patients demonstrate a reduction in endothelial vasodilators (EDV) in both peripheral and coronary arteries. Some of the pathophysiological stimuli and consequences are shown in Figure 9. ED begets numerous vascular consequences, setting up a vicious cycle of increasing ED (Figure 10). Therefore, leads to inappropriate vasoconstriction, reduced NO, PGII, PGE, PGE3, increased platelet aggregation, thrombosis, vascular hypertrophy, proliferation, oxidative stress and vascular permeability that result in numerous vascular diseases such as atherosclerosis, hypertension, CHD and CVA.

HYPERTENSION AND OXIDATIVE STRESS IN ANIMAL MODELS

Excess production of oxidants (reactive oxygen species [ROS]) and a deficiency of antioxidant systems contribute to hypertension and ED with endothelial-dependent impairment of vascular relaxation in the spontaneously hypertensive rat (SHR). In fact, in the spontaneously hypertensive rat (SHR), the increase in reactive oxygen species (ROS) precedes the development of hypertension. Increased ROS production in vitro and in vivo has been demonstrated in several animal models of hypertension. These studies suggest that ROS participate in the development and maintenance of hypertension in the SHR. These ROS may be an early event in the pathogenesis of human hypertension.

The increased ROS in the SHR inactivates NO leading to vasoconstriction and hypertension. Superoxide anion ($\text{O}_2^-$) and other ROS have been shown to act avidly with NO and cause its inactivation with subsequent ED. There is marked upregulation of renal, cardiac and vascular expressions of endothelial (eNOS), inducible (iNOS) and NOS proteins in young SHR. This is due to ROS mediated reduction in NO bioavailability and reduced negative feedback on the regulation of NOS expression.
The proposed mechanisms of ROS induced hypertension in the SHR include inactivation of endothelium-derived NO,76,78,84 nonenzymatic generation of vasoconstrictive F-2-isoprostanes from arachidonic acid peroxidation79 and depletion of the NOS cofactor-tetrahydrobiopterin (BH4).77 Angiotensin II (A-II) will increase superoxide production (O2-) by the NAD(P)H oxidase in endothelial cells,68,85,86

Antioxidant administration ameliorates hypertension in the SHR supporting the concept that ROS play a role in the genesis and maintenance of hypertension.26,78,79,87,88,89 Antioxidant treatment with tempol, a cell-permeable superoxide dimutase (SOD) to SHR lowers BP and increases NO.78 Antioxidant treatment with ascorbic acid, glutathione, amino-triazol and vitamin E also reduces BP in SHR.67 The vitamin E fortified diet in SHR will increase NO, reduce endothelial nitric oxid (eNOS) and lower BP.69 Numerous antioxidants have the same effect, but these effects are not due to a nonspecific action of the antioxidant therapy. Antioxidant administration in the normotensive animal in the absence of oxidative stress does not change BP, urinary NO excretion, or NOS expression.69,83,91

There is emerging evidence that dietary factors, nutrients, vitamins and antioxidants play an important role in modulating endothelial dysfunction. Specifically, essential fatty acids (EFA), vitamins C and E, folic acid, arginine, coenzyme Q10 and others have a beneficial effect on endothelial function and possibly in preventing cardiovascular disease.92,93

HYPERTENSION AND OXIDATIVE STRESS IN HUMANS

Oxidative stress with an imbalance between ROS and the antioxidant defense mechanisms may contribute to the etiology of human hypertension, its initiation, maintenance, pathogenesis, pathophysiology and cardiovascular complications.26,27,28,30,93 Oxidative stress has been implicated in many hypertensive disorders including lead-induced,83,94,95,96 uremic, cyclosporin induced,97,98,99,100 salt-sensitive,101,102 preeclampsia, essential hypertension,27,103,104,105,106,107 dia-betes mellitus108,109 and in hypertension induced by high fat, high refined carbohydrate diets.110,111,112,113

Hypertensive patients have an impaired endogenous and exogenous antioxidant defense mechanism.27,28,29,30,114,115,116,117,118,119,120,121 This includes increased lipofuscin,27,28,30,114 increased lipid peroxidation,115,116 elevated plasma malondialdehyde (MDA) (p < .05),27,28,30,114,116 reduced superoxide dismutase (SOD) in erythrocytes (p < .005)115,116 and plasma,27,116 reduced glutathione peroxidase (p < .05),28,116,118 reduced vitamin A (p < .05),114,116 reduced vitamin C,114 reduced copper (p < .005),116 reduced vitamin E (p < .001),114,115,116 lower NO levels,27 and polyunsaturated fatty acids (PUFA) in red cell membranes,28,120 reduced glutathione,28,29 normal to reduced selenium levels,116,121 and increased plasma hydrogen peroxide (H2O2) production.119,122

In addition, hypertensive patients have more oxidative stress with more ROS produced and a greater than normal response to oxidative stress.57,68,85,86,115,116,119,122,123 This includes increased lipid peroxidation in serum and urine,115,116 increased MDA in serum and urine,27,28,30,114 elevated H2O2,119 increased production of O2- by polymorphonuclear leukocytes (PMN’s),27,68,115 increased NADPH oxidase activity86 and increased plasma zinc (p < .001).116

The proposed mechanisms of ROS-induced hypertension in humans is shown in Table 7.27,28,29,30,124,125,126 Nitric oxide exerts a negative feedback on NOS expression in cultured human endothelial cells.127 This leads to a compensatory upregulation of NOS by reducing NO bioavailability similar to that seen in lead,83,91,94 uremic100 and cyclosporin induced hypertension.97 An imbalance of vasodilators (such as NO) and vasoconstrictors (such as A-II) and their interaction with ROS contribute to the initiation and perpetuation of hypertension (Figure 11).128

Antioxidant deficiency and excess free radical production have been implicated in human hypertension in numerous epidemiologic, observational and interventional studies,84,86,93,123,129,130,131,132,133,134 Serum ascorbic acid (AA)
had the highest inverse association with systolic blood pressure (SBP) among risk factors for CVA, CVD, hypertension and hyperlipidemia.\textsuperscript{131,135} Ceriello et al\textsuperscript{132} demonstrated significant hypotensive effects with various antioxidants including ascorbic acid, glutathione and thiopronine in subjects with hypertension and diabetes mellitus. Normotensive control patients had no significant change in blood pressure.

Vitamin C increases endothelial vasodilation (EDVD) of epicardial coronary arteries in hypertensive patients.\textsuperscript{136} Intravenous vitamin C, thiopronine and glutathione each significantly reduced BP in hypertensive patients.\textsuperscript{132} In an eight week, placebo-controlled study of hypertensive subjects vs normotensive subjects,\textsuperscript{137} the SBP was significantly reduced by 9 mm Hg (p < .01) and urinary NO (UNox) was reduced. A regimen of vitamin C 500 mg qd, vitamin E 600 IU qd, beta-carotene 30 mg qd and zinc 200 mg qd was prescribed. Combinations of various antioxidants may have additive or synergistic effects in neutralizing ROS, increasing NO and improving EDVD and lowering BP.

A summary of the present research and conclusions of the role of oxidative stress in animal and human hypertension is shown in Table 8. The interrelations of neurohormonal systems, oxidative stress and cardiovascular disease is shown in Figure 12.\textsuperscript{138} The increased oxidative stress in human hypertension is thus a combination of increased generation of ROS, an exacerbated response to ROS and a decreased antioxidant reserve.\textsuperscript{138,139} The ED, arachidonic acid metabolites, renin angiotensin aldosterone system (RAAS) and sympathetic nervous system contribute to increased ROS. Reduced antioxidant reserve is due to low intracellular, extracellular, enzymatic and nonenzymatic antioxidants (Table 9).\textsuperscript{138}

Reactive oxygen species damage virtually every organelle, cell, and tissue in the body (Table 10).\textsuperscript{138,139} Their primary and ultimate mechanism of damage is intracellular calcium overload secondary to injury of subcellular organelles.\textsuperscript{138,139} ROS are actually second messengers that are involved in redox-sensitive transcription pathways mod-

---

### Table 8

**Hypertension and Oxidative Stress: Animal Models and Human Studies**

- Impaired anti-oxidant status (Endogenous and Exogenous)
- More oxidative stress, more ROS production
- Greater than normal response to oxidative stress
- ROS contribute to E.D. in aorta and resistance arteries with imbalance of vasconstrictors and vasodilators
- ROS is both cause and consequence of hypertension
- Antioxidants as single or combined agents reduce BP
- Inverse relationship between BP and antioxidant intake in observational and interventional studies.
- ED leads to VSM contraction, increased SVR and BP

### Table 9

**The Cytotoxic Oxygen Species and the Natural Defense Mechanisms**

<table>
<thead>
<tr>
<th>Reactive Oxygen Species</th>
<th>Antioxidant Defense Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free Radicals</td>
<td>Enzymatic Scavengers</td>
</tr>
<tr>
<td>O2•–</td>
<td>Superoxide dismutase</td>
</tr>
<tr>
<td>OH•</td>
<td>Hydroxyl radical</td>
</tr>
<tr>
<td>ROO•</td>
<td>Lipid peroxide (peroxyl)</td>
</tr>
<tr>
<td>RO•</td>
<td>Alkoxyl</td>
</tr>
<tr>
<td>RO2•</td>
<td>Thiyl</td>
</tr>
<tr>
<td>NO•</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>NO2•</td>
<td>Nitrogen dioxide</td>
</tr>
<tr>
<td>ONOO•</td>
<td>Peroxynitrite</td>
</tr>
<tr>
<td>C12H20F2N5</td>
<td>Nonenzymatic scavengers</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Vitamin C (ascorbic acid)</td>
</tr>
<tr>
<td>H2O2</td>
<td>Hydrogen peroxide</td>
</tr>
<tr>
<td>HOCI</td>
<td>Hypochlorous acid</td>
</tr>
<tr>
<td>ONOO–</td>
<td>Peroxynitrite</td>
</tr>
<tr>
<td>O2</td>
<td>Superoxide</td>
</tr>
<tr>
<td>O3</td>
<td>Superoxide</td>
</tr>
</tbody>
</table>

---

**Figure 12**

![Pathophysiologic Stimulus](image)

**Figure 12.**

Role of different extra-cardiac and extra-vascular systems in the genesis of oxidative stress and development of cardiovascular abnormalities. SNS, sympathetic nervous system; RAS, renin-angiotensin system.
ulating early and late gene induction with production of adhesion molecules, chemokines, cytokines, growth stimulatory genes, apoptotic genes and kinases in virtually all cells (Figure 13).\textsuperscript{140}

Touyz and Schiffrin\textsuperscript{141} studied vascular smooth muscle cells (VSMC) from peripheral resistance arteries of normotensive and hypertensive subjects. The generation of ROS, particularly H\textsubscript{2}O\textsubscript{2} by angiotensin II (A-II) is augmented in the VSMC of the hypertensive subjects. These NAD(P)H oxidase-dependent processes are associated with increased activation of phospholipase D (PLD), which may influence the redox-sensitive pathways through protein kinase C (PKC) and phosphatidic acid that contribute to vascular structural changes in human hypertension.

Essential hypertension is not only associated with oxidative stress, but the level of BP is partially related to the level of oxidative stress.\textsuperscript{142} Hypertensive patients compared to normotensive controls have significantly elevated GSSG/GSH index (oxidized glutathione / to reduced glutathione index), a measure of oxidative stress status, increased malondialdehyde (MDA), a lipid peroxidation product, elevated 8-OXO-2'-deoxyguanosine (a measure of DNA damage), and decreased activity of three major enzymatic antioxidants including superoxide dimutase (SOD), catalase (CAD) and glutathione peroxidase (GPX). These indicators of oxidative stress correlate with urinary albumin excretion (UAE), left ventricular mass index (LVMI) and partially to BP. Hypertension-induced target organ damage is related to the level of oxidative stress, but this is, in part, independent of BP levels.\textsuperscript{143}

### WEIGHT LOSS AND HYPERTENSION

Observational and experimental studies indicate that excess weight (body mass index [BMI] > 25) and visceral obesity (waist circumference over 35 inches [88 cm] in women and over 40 inches [102 cm] in men) is positively and directly associated with elevated blood pressure\textsuperscript{18} as well as dyslipidemia, diabetes, and CHD morbidity and mortality. Weight loss is one of the most effective means to significantly reduce BP\textsuperscript{18,144,145,146,147,148,149} in overweight hypertensive patients,\textsuperscript{150} overweight persons with high normal BP\textsuperscript{150} and in nonobese, hypertensive patients, or those with high normal BP.\textsuperscript{148} Reductions in BP occur before and often without weight loss to ideal body weight (IBW)\textsuperscript{18,151} related to the beneficial effects of calorie restriction.\textsuperscript{20} In the Trial of Hypertension Prevention I and II (TOHP I and II)\textsuperscript{150,152,153} a 4.4 kg weight loss resulted in a 7/5 mm Hg reduction in BP in the short and long term evaluation (36 months).\textsuperscript{150} A two pound weight loss reduced SBP 1 mm Hg and DBP 1.4 mm Hg. There was a direct weight-BP response relationship with greater weight loss resulting in greater BP reduction.\textsuperscript{150} Even a modest weight loss reduced the risk of developing hypertension.\textsuperscript{150} The short term and long term BP reduction persists as long as the weight is maintained.\textsuperscript{18,32,154,155} Unfortunately, only 13\% of subjects in TOHP II maintained weight loss at 3 years.\textsuperscript{150} In a meta-analysis of 11 clinical trials, the average BP reduction was 1.6 mm Hg per kg for SBP and 1.1 mm Hg per kg for DBP.\textsuperscript{18,151} Weight loss potentiates other nonpharmacologic and pharmacologic treatments\textsuperscript{149} for hypertension and improves concomitant risk factors (glucose, insulin resistance and lipids).\textsuperscript{5} The mechanisms\textsuperscript{151} include lower insulin levels, improved insulin resistance, reduced intravascular volume and sympathetic nervous system activity with concomitant increased parasympathetic nervous system activity, decreased systemic vascular resistance, sodium/water diuresis, lower plasma renin and aldosterone levels, improvement in sleep apnea and decreases in levels of tumor necrosis factor alpha (TNF-a), macrophage migration-inhibitory factor (MMIF), interleukins and cytokines,\textsuperscript{20,156,157,158,159,160,161,162,163,164,165,166,167}

In view of the crucial importance of a balance of macronutrients (protein, fats, carbohydrates) and micronutrients (Na\textsuperscript{+}, K\textsuperscript{+}, Mg\textsuperscript{++}, Ca\textsuperscript{++}, vitamins and antioxidants) in preventing and controlling BP through various pathophysiological pathways, weight loss should be achieved without imposing any nutritional deficiencies.\textsuperscript{20} These goals were achieved in the HOT Study (Hypertension Optimal Treatment) at 30 months in which the weight loss group used fewer antihypertensive medications to achieve the same BP level as the control group.\textsuperscript{149}

<table>
<thead>
<tr>
<th>Table 10\textsuperscript{138,139}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oxidative Stress and CV Disease</strong></td>
</tr>
<tr>
<td><strong>ROS EFFECTS</strong></td>
</tr>
<tr>
<td>• Lipid Peroxidation: (PUFA in membrane lipid bilayer)</td>
</tr>
<tr>
<td>• Protein Oxidation: induces lipid and CHI0 auto-oxidation proteolysis</td>
</tr>
<tr>
<td>• Carbohydrate Oxidation</td>
</tr>
<tr>
<td>• DNA oxidation and damage</td>
</tr>
<tr>
<td>• Organic molecule oxidation</td>
</tr>
<tr>
<td>• Genetic machinery and gene expression</td>
</tr>
<tr>
<td>• Transcription factors and DNA synthesis</td>
</tr>
</tbody>
</table>

### Relative Risk for Coronary Heart Disease According to Levels of Physical Activity\textsuperscript{*}

<table>
<thead>
<tr>
<th>Energy expended in exercise each week (in KJ)</th>
<th>&lt; 2100</th>
<th>2100-4199</th>
<th>4200-8599</th>
<th>8400-12,599</th>
<th>≥ 12,600</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of men</td>
<td>2002</td>
<td>3584</td>
<td>3481</td>
<td>2140</td>
<td>2534</td>
</tr>
<tr>
<td>Relative CHD risk</td>
<td>1</td>
<td>0.9</td>
<td>0.81</td>
<td>0.8</td>
<td>0.81</td>
</tr>
</tbody>
</table>

\* 1983 through 1997

Relative risk adjusted for age, body mass index, alcohol intake, hypertension, diabetes mellitus, smoking status, and early (< 45 y) parental death.
EXERCISE AND HYPERTENSION

Regular aerobic exercise significantly reduces established BP, glucose, lipids, sympathetic nervous system (SNS) activity; it reduces the risk of developing hypertension, reduces cardiovascular disease risk, lowers CHD risk, and decreases all-cause mortality. A meta-analysis of 13 controlled studies of regular exercise found a mean reduction in BP of 11.3 mm Hg/7.5 mm Hg. A regimen of 5 to 7 days a week of exercise at 50 to 75% of VO2 max (maximum oxygen consumption) for 30-45 minutes daily was required to sustain this effect. In a recent study by Sesso et al, an expenditure of 4,200 Kcal per week resulted in the optimal decrease in CHD risk. Increases in exercise above this level to over 12,600 Kcal per week did not further reduce CHD beyond the 19% reduction noted at 4,200 Kcal per week (Table 11). Exercise increases eNOS and NO, improves endothelial function in coronary and systemic circulation, which improves coronary artery blood flow to the ischemic myocardium, decreases systemic vascular resistance (SVR) and reduces BP.

SMOKING AND TOBACCO

Cigarette smoking is a major risk factor for cardiovascular disease and hypertension. A significant increase in blood pressure accompanies smoking. Smoking reduces the protection against cardiovascular disease from antihypertensive therapy. The cardiovascular benefits of discontinuing tobacco use can be seen within one year in all age groups. The lower amounts of nicotine contained in smoking cessation aids usually will not raise blood pressure. Smoking causes vasoconstriction, increased sympathetic nervous system (SNS) activity, ED, hypertension, CVA and CHD. All tobacco products should be completely eliminated.

EVOLUTIONARY NUTRITION

We have evolved from a pre-agricultural, hunter-gatherer society to one of commercial agriculture and highly processed, refrigerated and fast foods. This has imposed upon humans an unnatural and unhealthy nutritional selection process. Our genetic makeup is 99.9% that of our Paleolithic ancestors, yet our nutritional, vitamin and mineral intakes are vastly different. The macronutrient and micronutrient variations of protein, fats, carbohydrates, fiber, sodium, potassium, magnesium and various vitamins and minerals contribute to the higher incidence of hypertension and other cardiovascular diseases through a complex nutrient-gene interaction (Table 12). Poor nutrition, coupled with obesity, a sedentary lifestyle and minimal exercise, has resulted in an exponential increase in nutritionally-related pathophysiology and disease. In particular, the high Na+/K+ ratio of modern diets has contributed to hypertension, stroke, CHD, CHF and renal disease. In addition, the relatively low intake of omega-3 polyunsaturated fatty acids (PUFA), increase in omega-6 PUFA and trans fatty acids, has contributed to the high incidence of CHD, hypertension, and other cardiovascular diseases.

Table 12

Evolutionary Nutritional Impositions

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Paleolithic Intakes</th>
<th>Modern Intakes</th>
</tr>
</thead>
<tbody>
<tr>
<td>K⁺</td>
<td>&gt; 10,000 meq / day (256 Gms)</td>
<td>150 meq / day (6 Gms)</td>
</tr>
<tr>
<td>Na⁺</td>
<td>&lt; 50 mmol / day (1.2 Gms)</td>
<td>175 mmol / day (4 Gms)</td>
</tr>
<tr>
<td>Na⁺ / K⁺</td>
<td>&lt; 0.13 / day</td>
<td>&gt; 0.67 / day</td>
</tr>
<tr>
<td>Protein</td>
<td>&gt; 100 Gms / day</td>
<td>9 Gms / day</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>41%</td>
<td>40% - 50%</td>
</tr>
<tr>
<td>Fat</td>
<td>22%</td>
<td>30% - 40%</td>
</tr>
<tr>
<td>P/S Ratio</td>
<td>1.4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Table 13

Examples of Nutrient - Gene Interactions

- PUFA (Omega-3): Cell differentiation, Growth, Energy metabolism, Energy balance and insulin sensitivity
- Sodium
  - Quil, (Quantitative Trait Loci) in rat chromosome 19 and 12 with HSP (Heat Shock Protein) 27 gene → stress response and SNS (Sympathetic Nervous System) activity with Na⁺ intake
  - Most recent study: Na⁺ → ETOH increases in BF more with low Ca⁺⁺ intake
- Angiotension Gene: AS vs GC Na⁺ / K⁺ response: AS genotype had best response to low Na⁺ intake, as well as to weight loss (BOTH) and BASH diet
- Vasopressin
- Lower BP
- ↓ CVA in SHR (Spontaneously Hypertensive Rat) and humans
- ↓ Na⁺ / K⁺ ATPase in VSMC (Vascular Smooth Muscle Cells) and SNS, increase in urinary sodium
- Obesity: ↓ leptin receptor gene → ↓ leptin → ↓ SNS → ↑ BP
- Fetal Growth Retardation and Low Birth Weight due to Abnormal GLUT-4 (Glucose Transporter) gene

Figure 14

Nutrient-Gene Interactions and Gene Expression (“The Interaction of Nature and Nurture”)

- Nutrients determine amount and activity of specific proteins produced by human genome by functioning as regulators of:
  - A. Gene Transcription
  - B. Nuclear RNA processing
  - C. Messenger RNA stability and degradation

Determine and influence

• Energy Metabolism
• Cell Differentiation
• Cell Growth

April 2002 JANA Supplement No. 1
cicular and metabolic disorders such as diabetes mellitus and hyperlipidemia.\textsuperscript{188,189,190,191,192}

**NUTRIENT-GENE INTERACTIONS**

The human genetic pool remains basically unchanged for the past 35,000 years.\textsuperscript{181} We are still genetically geared to a pre-agricultural, hunter-gatherer nutritional and exercise lifestyle. This includes, at a minimum, a low Na\textsuperscript{+} intake (less than 2 grams per day), high K\textsuperscript{+} intake (over 500 mEq per day), a K\textsuperscript{+}/Na\textsuperscript{+} ratio > 5:1, low saturated fat (less than 10\% total calories), high omega-3 PUFA, more monounsaturated fats with a total fat intake of 20-25\% of total calories, high fiber (> 50 grams per day), moderate protein (30-35\% total calories), moderate unrefined carbohydrate (35-40\% total calories), no trans fatty acids and regular aerobic and resistance exercises performed daily.\textsuperscript{33,148,182,186,187,188,189,190,191,192,193} Perhaps some alternating feasting and hunger would be healthful as well, as this was part of the Paleolithic lifestyle.

Nutritionally-related diseases such as diabetes mellitus, CHD, hypertension, CHF, cancer, and hyperlipidemia have reached epidemic levels in the U.S.\textsuperscript{182,184} This is due, in part, to the drastic change in the amount and frequency of human exposure to selected undesirable and unhealthy macro- and micronutrients.\textsuperscript{183}

Nutrients are powerful, influential factors to which the human genome is exposed. These nutrients determine the amount and activity of specific proteins by functioning as regulators of gene transcription,\textsuperscript{182,184,194,195} nuclear RNA processing\textsuperscript{182,184,196} and messenger RNA stability and degradation.\textsuperscript{182,184,197} These factors, in turn, determine and influence energy metabolism, cell differentiation and cell growth\textsuperscript{182} (Figure 14).

The clinical outcomes of nutrient regulation of gene expression can be beneficial with reduction of cardiovascular disease, BP, glucose and lipids or detrimental with an increase in cardiovascular disease, BP, glucose and lipids\textsuperscript{184} (Figure 15). The omega-3 PUFA are strong determinants of cell growth, energy metabolism, energy balance and insulin sensitivity.\textsuperscript{182,198,199} A ratio of omega-3 to omega-6 PUFA of between 1:1 to 4:1 is considered beneficial to cardiovascular health and approaches that of our Paleolithic ancestors and the Inuit Eskimos.\textsuperscript{181}

Some examples of nutrient-gene interactions are shown in Table 13 for PUFA,\textsuperscript{182,198,199} the Dietary Approaches to Stop Hypertension (DASH) diet\textsuperscript{193,200} and the Trials of Hypertension Prevention (TOHP) diet,\textsuperscript{152,153} sodium\textsuperscript{152,153,201,202,203}, potassium,\textsuperscript{201,203} obesity,\textsuperscript{201} and fetal growth retardation.\textsuperscript{201}

**GENETICS OF HYPERTENSION**

Hypertension is a complex interplay of susceptibility genes and environmental factors.\textsuperscript{201} It is a multifactorial trait with multiple genes (polygenetic) involved in BP regulation and pathogenesis.\textsuperscript{203,204} The multiple genes contribute to the specific phenotypes through epistasis (interactive effect of nonallelic genes on a phenotype) and pleiotropy (simultaneous effects of a single gene on multiple phenotypes).\textsuperscript{201} The genetic-environmental action is not parallel, but is an interaction.\textsuperscript{201}

Hypertension before age 55 is 3.8 times more common in patients with a positive family history than in those with
a negative family history. Approximately 30-60% of the BP variations in a population are secondary to genetic factors. The remainder are secondary to the environment. Monogenic hypertension due to a single gene mutation is quite rare and includes apparent mineralocorticoid excess (AME), Liddle’s Syndrome (LS) and glucocorticoid suppressible hyperaldosteronism (GSH).

Examples of genetic-environmental factors and interactions are shown in Table 14. An inherited perturbation in renal sodium handling plays a significant role in genetic hypertension. More than 50% of hypertensive patients are “salt sensitive,” demonstrating increases in MAP of about 10% with increased sodium intake and reduction in BP with sodium intake reduction. Potassium, magnesium and calcium are natriuretic and ameliorate salt-sensitive hypertension; whereas refined carbohydrates, saturated fats and trans fatty acids have anti-natriuretic and hypertensive potential.

In the Trials of Hypertension Prevention I (TOHP-I), the G-6A angiotensinogen gene was associated with responsiveness to dietary interventions. Caucasians with the AA genotype of G-6A had lower BP and reduced incidence of hypertension from either reduced sodium intake or weight reduction compared to the GA or GG genotypes. Similarly, in the (DASH-I,DASH-II) studies, the best BP response occurred in individuals with the AA genotype, and the least response was in those with the GG genotype.

**NUTRITIONAL INTERVENTION TRIALS IN HYPERTENSION**

Numerous nutritional intervention trials for the prevention and treatment of hypertension have demonstrated significant reductions in BP and target organ damage in hypertensive subjects, prevention of progression to higher BP in mildly hypertensive or subjects with high normal BP levels and reduction in antihypertensive medication use (Table 15). The Trials of Hypertension Prevention (TOHP-I) noted significant reductions in BP with various lifestyle changes over a six month period (Figure 16). The combination of weight loss and sodium restriction in TOHP-II resulted in a 60% reduction in incident hypertension at six months.

A recent meta-analysis of clinical nutritional and lifestyle changes evaluated the effects of numerous interventions on systolic BP (Table 16). The most effective intervention was the DASH diet followed by exercise, weight loss, sodium restriction and fish oil supplements. The least effective were increased intake of magnesium, calcium and potassium, or reduction in alcohol intake. This meta-analysis and other nutritional/diet studies emphasize the importance, the additive or synergistic effect of multiple nutrients, whole food and whole food concentrates with their nutrient combinations in a natural complex form to reduce BP and CVD.

**SINGLE VERSUS MULTINUTRIENT EFFECT**

Single nutrient effects such as only sodium reduction or only increased intake of calcium, potassium or magnesium were not as effective in reducing BP as were seen in the Mediterranean diet, the Cardiovascular Risk Reduction Dietary Intervention Trial (CVR-DIT), the Treatment of Mild Hypertension Study (TOMHS), the DASH-I,DASH-II diets, the Vanguard Study, or the China Trial.

The Mediterranean diets have effectively reduced BP, cardiovascular disease and MI. The Cardiovascular Risk Reduction Dietary Intervention Trial (CVR-DIT), the Treatment of Mild Hypertension Study (TOMHS), the DASH-I,DASH-II diets, the Vanguard Study, or the China Trial.
reductions in BP, lipids, glucose, homocysteine levels and weight, with a concomitant increase in quality of life and increase in nutrient levels in the blood. In subjects with hypertension alone, the average reduction in BP was 6.4/4.2 mm Hg. In subjects with hypertension and hyperlipidemia, the reduction in BP was 12.4/7.2 mm Hg. These data suggest that subjects with more cardiovascular risk factors and greater vascular damage (more ED or reduced aortic compliance) have the greatest benefit from nutritional intervention. A five kg weight loss was maintained in most subjects at the end of four years.215

The DASH-I combination diet and the Treatment of Mild Hypertension Study (TOMHS) diets reduced BP to levels that can be achieved by drug therapy in patients with mild hypertension (i.e. 10.7/5.2 mm Hg).193,208,216 Both diets emphasize eating fruits, vegetables, grains and low fat dairy products similar to vegetarian diets. Observational and prospective clinical trials consistently show that vegetarians have lower rates of hypertension,241 lower BP levels18,217,241 and do not have the steep rise in systolic BP with age.241 Vegetarians have mean arterial pressures of 10-15 mm Hg lower than non-vegetarians; and among vegetarians, those with the strictest vegetarian diets (no animal products) had the lowest BP.239,240,241,242 The mechanism of BP reduction may be due to a combination of factors including combinations of natural micronutrients (K+, Mg++, Ca++, Na+), macronutrients such as MUFA, PUFA, low saturated and trans fatty acids, reduced total fat, elevated P/S ratio and fiber.18,217,239,243,244 Both PUFA and MUFA incorporate into lipid membranes, improve fluid characteristics, permeability and increase Na+/K+ ATPase.243 In addition, the omega-3 fatty acids increase vasodilatory prostaglandins, reduce systemic vascular resistance and lower BP.244

Approximately 15 to 60% of hypertensive patients withdrawn from antihypertensive drugs remain normotensive for nine months to three years following strict lifestyle modifications of alcohol and Na+ restriction, weight loss and other nutritional and exercise counseling.218,219,220,221,222,223,224 Two models of hypertension prevention have been proposed.18 Lifestyle modifications may cause a downward shift in age-related rise in blood pressure without a change in slope or cause a downward shift in age-related rise in blood pressure with a change in slope (Figure 17).

The Linxian China Randomized Nutritional Intervention Trial of 29,584 subjects over five years showed variable results on hypertension, stroke, and total mortality depending on the nutritional supplement that was used.346 Subjects receiving Factor C (molybdenum and vitamin C) or Factor B (riboflavin and niacin) had small, but insignificant decreases in SBP and DBP of 0.50/0.24 mm Hg or 0.57/0.37 mm Hg respectively. Subjects receiving Factor D had reductions in total mortality of 9%, cancer reduction mortality of 13%, and stroke reduction of 9%. Factor D contained lipid soluble antioxidants and vitamins including beta-carotene, alpha-tocopherol, and selenium.
WHOLE FOOD BASED CONCENTRATES: FRUIT, VEGETABLE, AND FIBER EXTRACTS

Combinations of natural phytonutrients in a balanced form appears to provide better antioxidant protection, BP and CVD reduction than single “bullet type” nutrient supplementation as has been discussed. Whole food concentrates of fruits, vegetables and fiber may provide additional nutrient value to the recommended eight to ten servings of fruits, vegetables and grains a day (about 400 grams/day) or ensure better nutrition in the form of an “insurance policy” when dietary intake is suboptimal for a variety of reasons. Several prospective clinical human trials have been published or are in progress on such a product. These studies in humans have shown significant increases in serum and lymphocyte antioxidant and vitamin levels following oral ingestion, reduced oxidative stress, weight reduction with increased lean body mass and reduced total body fat, improved cellular immune function in lymphocytes, reduced DNA damage in lymphocytes, improved brachial artery flow-mediated vasodilation and improved endothelial function, and a reduction in homocysteine and BP levels. A two-year prospective trial is ongoing to evaluate the effects of this whole food concentrate on CHD regression or stabilization by Electron Beam Tomography (EBT).

THE DASH DIETS (DASH-I AND DASH-II-SODIUM) (Dietary Approaches to Stop Hypertension)

The DASH-I diet published in 1997 was a landmark nutritional trial in reducing blood pressure in hypertensive patients. The DASH-II sodium diet published in 2001 confirmed the value of DASH-I, but proved that moderate to severe sodium restriction further enhanced BP reduction. These nutritional studies are so important in the nonpharmacologic management of hypertension that they will be presented in detail.

The DASH-I diet was a two-month, multicenter, randomized, controlled prospective clinical trial of 379 subjects with borderline or Stage I hypertension (SBP < 160 mm Hg and DBP 80-95 mm Hg), no concomitant diseases and on no antihypertensive drugs. The average age was 45 years, two-thirds were minorities (60% black, 6% other races and 34% white). The design of the study and prescribed nutrition for the three treatment groups, which included control subjects, the fruit and vegetable (F + V) group and the combined diet (C) group, are shown in Figure 18. After a three week control diet in all subjects, randomization was to one of the three treatment groups above for eight weeks. The sodium content remained the same in all three groups at three grams per day. All diets were prepared and were well tolerated with a 93% adherence rate. There was no change in alcohol intake, weight, or sodium excretion during the study. Subjects met weekly with the investigators.

Table 20

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of sodium intake to 50 mmol/day from current recommendations of 100 mmol/day</td>
<td>-5 mmHg</td>
<td>-3 mmHg</td>
</tr>
<tr>
<td>DASH combination diet with low sodium intake of 50 mmol/day lowers BP more in combination than either singly.</td>
<td>-10.7 mmHg</td>
<td>-5.2 mmHg</td>
</tr>
<tr>
<td>Level of dietary sodium had twice BP reducing effect with the control diet than with DASH diet (p &lt; 0.001)</td>
<td>-8.9 mmHg</td>
<td>-4.5 mmHg</td>
</tr>
<tr>
<td>BP reductions occurred in all patients regardless of age, gender, ethnicity, or BP level (normals)</td>
<td>-11.5 mmHg</td>
<td>-6.8 mmHg</td>
</tr>
<tr>
<td>Hypertensive patients, blacks and women had greatest BP reductions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Na+ intake attenuated the hypotensive effects of K+ and Ca++</td>
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</tbody>
</table>

Table 21

<table>
<thead>
<tr>
<th>Summary of BP Reductions in DASH-I and DASH-II Na+ Diets Hypertensive Patients and Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>DASH-I Overall Combination Diet vs Control Diet</td>
</tr>
<tr>
<td>DASH-I Hypertensive Pts. Comb. Diet vs Control Diet</td>
</tr>
<tr>
<td>DASH-I Overall Comb. Low Na+ DASH Diet vs vs. Control high Na+ Diet</td>
</tr>
<tr>
<td>DASH-I Hypertensive Pts. Comb. Low Na+ DASH Diet</td>
</tr>
</tbody>
</table>

The results of this clinical trial (shown in Tables 17, 18 and Figure 19) demonstrate significant reductions in BP with controlled feeding and the described dietary modifications of increasing whole grains, nuts, poultry, fish, fruits, vegetables, K+, Mg++ and Ca++ while reducing intake of saturated and trans fatty acids, red meat, sweets, sugars and other refined carbohydrates. The hypertensive subjects on the combined diet had the greatest BP reduction of 11.4/5.5 mm Hg. Minority subjects, especially blacks, had greater reductions in BP compared to white subjects, and hypertensive subjects had greater BP reductions than normotensive subjects. Urinary Mg++ and K+ increased in the “F + V” and “C” groups, while urinary Ca++ decreased in the “F + V” group. The urinary Na+ remained constant in all three groups.

The reduction in BP occurred immediately, reaching near maximum levels at two weeks, but was sustained throughout the eight-week study. In addition, the quality of life improved in subjects on the “F + V” and “C” diets. The combined treatment group had reductions in BP that were equal to that obtained with pharmacologic treatment of mild hypertension. DASH-I emphasizes the importance of combined nutrients as they occur in natural food.

The DASH-II diet took the DASH-I diet one step further, proving that moderate to severe Na+ restriction...
**DASH-I: Trial Design**

- Borderline or Stage-I hypertension (SBP < 160, DBP 80-95)
- Age average 45 yrs; 2/3 minorities n=379
- No Anti-hypertensive drugs, otherwise healthy

**Protocol**

- **Control diet x 3 weeks (C)**
  - Na+ = 3 Gms / day
  - K+, Mg++, Ca++ = 25% U.S. average
  - Macronutrients = U.S. average (F + V 4 servings)
  - Na+ / K+ Ratio = 1.7
  - Fiber = 9 Gms / day

- **Fruit + Vegetable diet (F + V)**
  - Na+ = 3 Gms / day
  - K+, Mg++, Ca++ = 75% U.S. average
  - F + V = 8.5 servings / day
  - Na+ / K+ Ratio = 0.7
  - Fiber = 31 Gms / day

- **Combined Diet (Comb)**
  - Na+ = 3 Gms/day
  - K+, Mg++, Ca++ = Same (75%) US ave
  - F + V = 10 servings / day
  - Na+ / K+ Ratio = 0.6
  - Fiber > 31 Gms / day
  - Low Fat Dairy = 2.7 servings / day

8 Weeks (all Diets)

---

**Mean Systolic and Diastolic BP at baseline and during each intervention week, according to Diet for 379 Subjects**

- **Control Diet**
- **Fruits and Vegetable Diet (F + V)**
- **Combination Diet**

---

**DASH-II Sodium Diet: Results**

- α-Tocopherol inhibits thrombin-induced endothelin secretion in vitro at least partly through inhibition of PKC

- **Decreased OxLDL**

---

**Vitamin E: Mechanism in Hypertension and Vascular Disease**

- Insulin Sensitivity Improves
- Increased Total Antioxidant Status
- Increased NOS and NO
- Increased membrane and intracellular Mg++
- Increased Serum Glutathione Levels
- Reduces OxLDL

---

**Effect of Dietary Na+ Intake on Subgroups in the Control & DASH Diet groups**

- The error bars represent the 95 percent confidence limits of the change in BP for each subgroup. Hypertension was defined as an average SBP of 140 to 159 mmHg and average DBP of 90 to 95 mmHg during the three screening visits. The “other” category of race and ethnic group is composed primarily of non-Hispanic whites. Asterisks (p < 0.05), daggers (p < 0.01), and double daggers (p < 0.001) indicate significant differences between levels of sodium intake.

---

**Effects of K+ Supplementation on BP in Trials that Enrolled Predominantly Blacks (>80%) or Whites: Results of a Meta-analysis**

- * = P < 0.05 (main effect)
- † = P < 0.05 (interaction)
reduced BP even more in all three study groups.\textsuperscript{187} This was a multicenter, randomized, controlled prospective study of 412 subjects on either a control diet or one of three DASH-Na\textsuperscript{+} diets for 30 days (150 mmol, 100 mmol or 50 mmol Na\textsuperscript{+} intake). The SBP and DBP reductions were significant with each incremental decrease in Na\textsuperscript{+} intake (Figure 20, Table 19). The important conclusions and results of this study are shown in Table 20. Hypertensive subjects, blacks and women had the greatest BP reductions (Figure 21).

A comparison of the relative BP reduction in DASH-I and DASH-II in hypertensive subjects is shown in Table 21. The net BP reduction versus the control patient reduction was greatest in the DASH-II combination, low Na\textsuperscript{+} (50 mmol) diet (-11.5/6.8 mm Hg).\textsuperscript{187,193} The message from these two studies is clear. Hypertensive patients can achieve significant BP reductions that are equivalent to drug therapy used in mild hypertensive patients by combining a more severe Na\textsuperscript{+} restriction of 50 mmol/day with the combination DASH-I diet. These benefits are immediate, sustainable, inexpensive, and improve nutrient levels and the individual’s quality of life.

\textbf{VANGUARD STUDY}

Resnick and Oparil et al\textsuperscript{225} recently published an important, unique and provocative clinical hypertension nutrition trial that confirms the results of DASH-I, DASH-II and other nutritional intervention trials, and added a new dimension by measuring biochemical parameters. Seventy-one untreated hypertensive or hypertensive-hyperlipidememic patients were given a prepared meal plan, CCNW (Campbell Center for Nutrition and Wellness), and compared to 87 normotensive, hyperlipidemic control subjects on a self-selected diet based on nutritional counseling for 10 weeks in a multicenter, randomized, controlled trial.

The BP fell significantly more in the hypertensive compared to the normotensive patients, -8/5 mm Hg vs -2/-2 mm Hg (p < 0.0001) respectively and on the CCNW versus the self-selected diet (\textcopyright SBP/\textcircled DBP = p = 0.033/p = 0.002). Nutritional-induced weight loss had the highest correlation with BP change (SBP p < 0.0001 and DBP p < 0.0001). Some of the changes in SBP were correlated with fasting glucose (p = 0.009) and cholesterol (p = 0.006) in the multivariate analysis of the weight change effect on BP. Independent of weight, the nutritional-induced reduction in SBP significantly correlated with changes in urinary potassium excretion (p < 0.001), urinary magnesium excretion (p < 0.003), urinary calcium to sodium ratio (p < 0.021), serum potassium (p = 0.002), serum phosphorous (p = 0.001), parathyroid hormone (PTH) (p = 0.0006) and 1.25 dihydroxy vitamin D (1.25 vitamin D) (p = 0.017), but not to sodium per se (NS).

These results confirm the ability of a nutritionally sound diet to reduce BP, and also the importance of, and additive effects of, multiple nutrients, minerals and other dietary components in BP control. All study subjects on both diets had significant reductions in BP, but the CCNW diet had the largest effect especially in the combined hypertension-hyperlipidemic patients. The improved mineral metabolism mediated by vasoactive mineral-regulating hormones such as the parathroid (PTH) and 1,25 vitamin D correlated significantly and positively with urinary K\textsuperscript{+}, Mg\textsuperscript{++} and Ca\textsuperscript{++}/Na\textsuperscript{+} ratio. The data are consistent with the DASH Diet Trial reflecting additive effects of multiple dietary components such as K\textsuperscript{+}, Mg\textsuperscript{++} and Ca\textsuperscript{++}, but supporting the significance of Na\textsuperscript{+} only in relation to other minerals such as Ca\textsuperscript{++}, rather than as Na\textsuperscript{+} per se. The enhanced antihypertensive effect of a multinutritional diet as opposed to single specific nutrient was seen in patients with more vascular disease or more CV risk factors (i.e. the hypertensive-hyperlipidemic patients). If these beneficial results can be sustained with a long-term nutrition program with education, nutritional counseling and possibly prepared meal plans, then hypertension control will be more easily achieved.

This trial and others\textsuperscript{182,187,193,209,216,225} have recently focused on the role of naturally occurring nutrients in whole food as opposed to isolated dietary components in BP reduction. This, as we shall see with a few exceptions, is the key to controlling BP and the hypertension syndrome.

\textbf{SODIUM (Na\textsuperscript{+})}

The average sodium intake in the U.S. is 5,000 mg per day though in some areas of the country people consume 15,000 to 20,000 mg per day.\textsuperscript{14} However, the minimal requirement for sodium is probably about 500 mg per day.\textsuperscript{14} Epidemiologic, observational and controlled clinical trials have clearly shown that an increased sodium intake is associated with higher blood pressure.\textsuperscript{256} A reduction in sodium intake in hypertensive patients, especially the salt-sensitive patients, will significantly lower blood pressure with average reductions of 4-6 mm Hg systolic BP and 2-3 mm Hg diastolic BP.\textsuperscript{18,24,187,257,258,259} The blood pressure reduction is proportional to the severity of sodium restriction.\textsuperscript{18,187,260,261}

In the Trial of Hypertension Program I study (TOHP-I),\textsuperscript{31} a 100 mmol sodium intake per day (2,400 mg) reduced the incidence of hypertension by 20% in a group of high risk subjects, improved hypertension control in elderly subjects on medications in the TONE Study,\textsuperscript{12} reduced cardiovascular disease in obese subjects\textsuperscript{186} and reduced proteinuria and progression of renal disease.\textsuperscript{18,261,262} The TOHP-II Trial had a mean BP reduction of 2.9 mm Hg ± 1.6 mm Hg with moderate sodium restriction.\textsuperscript{150} There was no rebound increase in sodium excretion at the end of intervention in TONE, indicating that the preferred amount of sodium in food is smaller after reduction in the sodium intake.\textsuperscript{155}

The effect of dietary sodium on BP is modulated by other components of the diet.\textsuperscript{20,228,245,263} A severe sodium restriction may concomitantly decrease other essential dietary compo-
nents such as calcium, potassium, fiber and protein that would adversely affect BP and cardiovascular risk. Sodium chloride-induced hypertension is augmented by diets low in potassium, calcium and magnesium and attenuated by high potassium, magnesium and calcium (especially Na+ sensitive). This is true only of sodium with chloride, not other anions. An increased dietary intake of simple carbohydrates also augments the BP response to sodium chloride. The DASH-II diet is particularly instructive in this regard.187 Gradual reductions in sodium from 150 mmol to 100 mmol to 50 mmol per day in association with a high fruit, vegetable and low fat dairy intake with adequate potassium, calcium, magnesium and fiber intake was the most effective in reducing BP.

Despite the enormous body of literature on “salt and hypertension”, debate still exists as to a true causal relationship. Nevertheless, sodium does have a major impact on cardiovascular, cerebrovascular and renal disease. Studies have documented a direct relationship between sodium intake and increased platelet reactivity, stroke (independent of BP), left ventricular hypertrophy, MI, CHF, sudden death and left ventricular filling. The renal plasma flow falls and glomerular filtration rate increase leading to an increase in intraglomerular capillary pressure, microalbuminuria, proteinuria, glomerular injury and renal insufficiency. Sodium also reduces arterial compliance independent of BP changes.

Salt sensitivity (≥ 10% increase in MAP with salt loading) is a key factor in determining the cardiovascular, cerebrovascular, renal and blood pressure response to dietary salt intake. Cardiovascular events are more common in the salt-sensitive patients than in salt resistant ones, independent of BP. This may reflect specific target organ sensitivity and vulnerability to sodium that is unrelated to BP. In addition, salt sensitivity is most pronounced in elderly patients with isolated systolic hypertension and it is modified by polymorphisms of the angiotensinogen gene. Salt sensitive patients do not inhibit their sympathetic nervous system activity or increase NO production with salt loading.

The evidence is very suggestive that reduction of dietary salt intake reduces target organ damage (brain, heart, kidney and vasculature) that is both dependent on the small BP reduction, and also independent of the decreased BP. However, it should be noted that higher sodium consumption has actually been associated with lower BP suggesting that nutritional deficiencies and relative serum levels or total body stores (K+, Mg++, Ca++, vitamins, antioxidants and essential fatty acids) and not excess sodium cause hypertension. On the other hand, strict dietary sodium restriction may increase the risk of nutrient, mineral, vitamin and antioxidant deficiencies due to a narrow and limited nutritional intake that could elevate BP.

Clearly, a balance of sodium with other nutrients is important, not only in reducing and controlling BP, but also in decreasing cardiovascular and cerebrovascular events.

In the Montreal Study on the relationship of Ca++ and Na++, salt intake influenced BP only in those with a low Ca++ intake. Increased calcium intake has a depressor effect to increased Na+ intake. Other studies have demonstrated that the response to calcium is closely linked to the effect of salt. The renal plasma flow falls and glomerular filtration rate increase leading to an increase in intraglomerular capillary pressure, microalbuminuria, proteinuria, glomerular injury and renal insufficiency. Sodium also reduces arterial compliance independent of BP changes.

POTASSIUM (K+)

The average U.S. dietary intake of potassium(K+) is 45 mEq per day with a potassium to sodium ratio of less than 1:2. The recommended intake of K+ is 650 mEq per day with a K+/Na+ ratio of over 5:1. Numerous epidemiologic, observational and clinical trials have demonstrated a significant reduction in BP with increased dietary K+ intake. The magnitude of BP reduction with a K+ supplementation of 60 to 120 mEq per day is 4.4 mm Hg systolic and 2.5 mm Hg diastolic in hypertensive patients. A high potassium intake is most effective in reducing BP in patients with diuretic induced hypokalemia, those with a high Na+ intake, patients with salt-sensitive hypertension, severe hypertension or a positive family history and patients who are of African American or Chinese descent. Alteration of the K+/Na+ ratio to a higher level is important in both antihypertensive as well as cardiovascular and cerebrovascular effects. High potassium intake reduces the incidence of cardiovascular and cerebrovascular accidents independent of the BP reduction. Improvements in vascular smooth muscle function and structure, natriuresis, modulation of baroreflex sensitivity, direct vasodilation, reduced vasoconstrictive sensitivity to norepinephrine and angiotensin II, increased serum and urinary kallikrein, increased Na+/K+ ATPase activity and DNA synthesis and proliferation in vascular smooth muscle cells and sympathetic nervous system cells are some of the proposed mechanisms for the beneficial cardiovascular, cerebrovascular and antihypertensive effects of K++.
men and women aged 35 to 64 years. This study confirmed that the higher the initial BP, the greater the response. Finally, it showed that the urinary sodium-potassium ratio correlates best with BP reduction as does the dietary sodium-potassium ratio\(^{265}\) compared to either urinary sodium or potassium individually.\(^{296}\)

In addition, K\(^+\) may have a Ca\(^+\)-conserving effect that would further minimize the effects of a high Na\(^+\) intake.\(^{299}\) The interactions of Na\(^+\), Ca\(^+\), K\(^+\) and Mg\(^++\) are more important in BP control than are isolated changes in one mineral.\(^{187,193,225,234,291,293,299}\)

**MAGNESIUM (Mg\(^++\))**

A high dietary intake of magnesium of at least 500-1,000 mg per day reduces BP in most of the reported epidemiologic, observational and clinical trials, but the results are less consistent than those seen with Na\(^+\) and K\(^+\).\(^{14,18,148,152,203,256,300-306}\) In most epidemiologic studies, there is an inverse relationship between dietary magnesium intake and BP.\(^{20,148,289,302,303,306,307,308,309,310,311}\) A study of 60 essential hypertensive subjects given magnesium supplements showed a significant reduction in BP over an eight week period documented by 24 hour ambulatory BP, home and office blood BP.\(^{301}\) However, in the TOHP-I Trial, magnesium had a small insignificant and inconsistent effect on BP.\(^{152}\) The intake of multiple minerals in a natural form such as Mg\(^++\), K\(^+\) and Ca\(^++\) is more effective than Mg\(^++\) alone in reducing BP.\(^{203}\) Magnesium may also be effective in acute MI and atherosclerosis.\(^{300}\)

Magnesium competes with Na\(^+\) for binding sites on vascular smooth muscle and acts like a calcium channel blocker (CCB), increases PGE\(_1\), binds in a necessary-cooperative manner with potassium, inducing (EDV) vasodilation and BP reduction.\(^{14,256,289,311,312,313}\)

Witteeman et al\(^{314}\) treated 91 middle-aged and elderly women with mild to moderate hypertension on no antihypertensive medications in a double-blind placebo controlled study given magnesium asparate-HCL, 20 mmol per day (485 mg of Mg\(^++\)) vs placebo for six months. The SBP fell 2.7 mm Hg (p < 0.18), DBP fell 3.4 mm Hg (p < 0.003), urinary Mg\(^++\) increased, but the lipid profile did not change. The BP response was not associated with baseline magnesium status.

Magnesium is an essential co-factor for the delta-6-desaturase enzyme that is the rate-limiting step for conversion of linoleic acid (LA) to gamma-linolenic acid (GLA).\(^{289,315,316,317}\) GLA elongates to form DGLA (dihomo-gamma-linolenic acid), the precursor of prostaglandin E\(_1\) (PGE\(_1\)), a vasodilator and platelet inhibitor.\(^{289,315}\) In hypomagnesemic states, insufficient amounts of PGE\(_1\) are formed, leading to vasoconstriction and increased BP.\(^{289,316}\)

Magnesium regulates both SBP, DBP, intracellular Ca\(^++\), Na\(^+\), K\(^+\) and pH as well as left ventricular mass, insulin sensitivity and arterial compliance.\(^{310,311}\) Newer techniques such as P-Nuclear Magnetic Resonance (NMR) and Mg\(^++\)-specific ion-selective electrodes (ISE) that measure intracellular and extracellular free levels of magnesium will enhance the understanding of the role of Mg\(^++\) in hypertension.\(^{310}\)

**CALCIUM (Ca\(^++\))**

While population studies show a link between hypertension and calcium,\(^{14,148,318}\) clinical trials that administer calcium supplements to patients have shown inconsistent effects on BP.\(^{18,319,320}\) Higher dietary calcium is not only associated with a lower BP, but also with a decreased risk of developing hypertension.\(^{148,321}\) A 23% reduction in the risk of developing hypertension was noted in those individuals on greater than 800 mg per day compared to those on less than 400 mg per day.\(^{148,322}\)

A recent meta-analysis of the effect of Ca\(^++\) supplementation in hypertensive patients found a reduction in systolic BP of 4.3 mm Hg and diastolic BP of 1.5 mm Hg.\(^{293,323,324}\) Foods containing Ca\(^++\) were more effective than supplements in reducing BP.\(^{293,324}\) Karanja et al\(^{325}\) assessed the effects of CaCO\(_3\) (calcium carbonate) vs calcium contained in the diet and found significant increases in magnesium, riboflavin and vitamin D in the dietary group that correlated with Ca\(^++\) intake. There is an additive or synergistic effect on BP reduction with combination minerals and vitamins as compared to Ca\(^++\) alone.\(^{187,193,225}\)

The TOHP-I tested the individual effects of several micronutrients and other dietary factors on BP.\(^{152}\) In hypertensive patients with a DBP of 80-89 mm Hg. Increases in dietary Ca\(^++\) and Mg\(^++\) had little effect on BP, whereas Na\(^+\) restriction and weight loss produced significant decreases in BP.\(^{152}\)

The response to Ca\(^++\) intake may be dependent on the population or hypertensive subtype that has been studied.\(^{203,321,326}\) Those patients with the most reduction in BP with Ca\(^++\) supplements include blacks, those with low-renin hypertension, the elderly, pregnant women (pregnancy-induced hypertension [PIH]), Na\(^+\) sensitive hypertensives, those on a high Na\(^+\) intake, type II DM and postmenopausal women.\(^{203,321,326}\)

The heterogeneous responses to calcium supplementation have been explained by Resnick.\(^{327}\) There are two underlying calcium-related mechanisms. One is salt-sensitive, low renin and calcium antagonist-sensitive, which is dependent on impaired cellular calcium uptake from the extracellular space. The other is salt-sensitive, renin-dependent and calcium-antagonist-insensitive, which is dependent on increased cellular calcium released from intracellular sites. Reduced dietary calcium may deplete calcium from all membrane storage sites causing a less stable membrane of vascular smooth muscle cells.\(^{327,328}\)
When calcium is present in optimal concentrations, it stabilizes vascular membranes, blocks its own entry into cells and reduces vasoconstriction. Calcium in combination with other ions such as Na⁺, K⁺ and Mg⁺⁺ provides ionic balance to the vascular membrane, vasorelaxation and reduced BP.

This “ionic hypothesis” of hypertension, cardiovascular disease and associated metabolic, functional and structural disorders is characterized by the following:

1. Increased intracellular free Ca⁺⁺ and reduced intracellular free Mg⁺⁺ which determine the relative vasoconstriction or vasodilation.

2. Elevated glucose and LDL-C increase the intracellular Ca⁺⁺ and/or lower intracellular Mg⁺⁺ in VSM cells.

3. Hypertension, insulin resistance and type II DM are characterized by increased intracellular Ca⁺⁺ and decreased intracellular Mg⁺⁺ in VSM cells and cardiac muscle.

4. The higher the PTH level, the greater the fall in BP and the greater the reduction in PTH and 1,25 vitamin D, the greater the BP reduction.

5. Salt-sensitive and Ca⁺⁺-sensitive hypertension have elevated intracellular Ca⁺⁺, PTH and 1,25 vitamin D, but low intracellular Mg⁺⁺.

6. Dietary Ca⁺⁺ reverses abnormal calcium indices and lowers BP.

7. Dietary Ca⁺⁺ suppressible hormones like PTH, 1,25 vitamin D are vasoactive and promote Ca⁺⁺ uptake in VSM cells and cardiac muscle.

8. Weight loss decreases intracellular Ca⁺⁺ levels.

9. Dietary Ca⁺⁺ reduces urinary Ca⁺⁺ excretion and 1,2 vitamin D plasma levels.

10. Mg⁺⁺ intake reduces tissue Ca⁺⁺ accumulation.

The overall effect of nutrition and diet on BP is thus determined by the net contribution of multiple nutritional components on cytosolic free mineral ions such as Ca⁺⁺ and Mg⁺⁺. Direct ionic effects on glucose or Ca⁺⁺ and ionic effects on hormones (PTH, 1,25 vitamin D) regulate these steady-state mineral concentrations.

**ZINC (Zn⁺⁺)**

Low serum zinc levels in observational studies correlate with hypertension as well as CHD, type II DM, hyperlipidemia (especially hypertriglyceridemia and low HDL-C), elevated lipoprotein a (Lp(a)), two-hour postprandial plasma insulin levels and possibly insulin resistance. Elderly hypertensives with very low plasma renin activity (PRA) have high urinary excretion of Zn⁺⁺ and low serum levels a condition partially corrected by the administration of oral calcium > 800 mg per day. There is a close relationship between Zn⁺⁺, Ca⁺⁺, Na⁺⁺, Mg⁺⁺ and K⁺ in various hormonal systems (SNS, RAAS) that modulate BP.

Galley et al administered antioxidants to 40 hypertensive and normotensive adult subjects in a randomized, double-blind, crossover design placebo-controlled study for eight weeks. The antioxidants administered were zinc sulfate 200 mg per day, ascorbic acid 500 mg per day, alpha-tocopherol 600 mg per day, and beta carotene 30 mg per day. The SBP decreased significantly in the hypertensive subjects (p < 0.01) and decreased in the normotensive subjects (p < 0.067). Increases in plasma levels of antioxidants and increased urine nitrate excretion occurred in the hypertensive subjects, suggesting an increased bioavailability of NO.

Bergomi et al evaluated Zn⁺⁺ and Ca⁺⁺ status in 60 hypertensive compared to 60 normotensive control subjects. An inverse correlation of BP and serum Zn⁺⁺ was observed, but there was a direct correlation with serum Ca⁺⁺. The BP was also inversely correlated to a Zn⁺⁺ dependent enzyme-lysyl oxidase activity. Zn⁺⁺ inhibits gene expression and transcription through nuclear factor kappa-beta (NFK-B) and activated protein-1 (AP-1). These effects plus those on insulin resistance, membrane ion exchange, RAAS and SNS effects may account for Zn⁺⁺ antihypertensive effects. Zinc intake should be between 15-30 mg per day.

**PROTEIN**

Observational and epidemiologic studies indicate an association between high protein intake and a reduction in BP in Japanese rural farmers, Japanese-American men in Hawaii, American men in two cohort studies, British men and women, Chinese men and women and American children. The protein source is an important factor in the BP effect; animal protein is less effective than nonanimal sources. However, lean or wild animal protein with less saturated fat and more essential omega-3 fatty acids may reduce BP, lipids and CHD risk. The Intermap Study, a large international observational study showed an inverse correlation of BP with total protein intake and with protein intake from nonanimal sources.

The Intersalt Study supported the hypothesis that higher dietary protein intake has favorable influences on BP. The study evaluated 10,020 men and women in 32 countries worldwide and found that SBP and DBP were 3.0 mm Hg and 2.5 mm Hg lower respectively on average for those whose dietary protein was 30% above the overall mean than for those 30% below the overall mean (81 gm/day versus 44 gm/day).

Fermented milk supplemented with whey protein concentrate significantly reduced BP in animal models (rats) and human studies. Kawase et al studied 20 healthy men...
given 200 ml of fermented milk/whey protein BID for eight weeks. The SBP was reduced (p < 0.05), HDL-C increased (p < 0.05) and TG fell (p < 0.05) in the treated compared to the control group. Natural bioactive substances in milk and colostrum including minerals, vitamins and peptides have been demonstrated to reduce BP. Milk ingestion increases protein, vitamins A, D and B₁₂, riboflavin, pantothenate, calcium, phosphorous, magnesium, zinc and potassium. These findings are consistent with the combined diet of fruits, vegetables, grains and low fat dairy in DASH-I and DASH-II studies in reducing BP.

Soy protein at intakes of 25 to 30 grams/day lowers BP and increases arterial compliance as well as reducing LDL-C and total cholesterol (TC) by 6 to 7% and reducing LDL-C oxidation. Soy contains many active compounds that produce these antihypertensive and hypolipidemic effects including isoflavones, amino acids, saponins, phytic acid, trypsin inhibitors, fiber and globulins.

Laplante et al recently evaluated the effects of genistein, an active ingredient in soy, on the BP of angiotensin-treated hypertensive rats. Blockade of tyrosine kinase (TK) pathway with genistein significantly reduced SBP (p < 0.05) when exposed to A-II infusion. In addition, the superoxide anion radical concentration in aortic tissue decreased (p < 0.05), and the extracellular signal-regulated kinases-mitogen activated protein kinases (ERK-MAPK) pathway activity was suppressed (P < 0.05). These results suggest that genistein lowers BP by decreasing ERK-MAPK activity and superoxide anion radical in A-II related hypertension. Other studies have shown that genistein inhibits tyrosine kinase activity, reduces ROS by a direct antioxidant effect or protects tyrosine phosphatases, which shifts the balance of protein phosphorylation-dephosphorylation reactions. Phosphorylation of proteins by tyrosine kinases and other protein kinases escalates signal transduction pathways, which induces growth promotion, platelet aggregation, VSM hyperplasia and hypertrophy, increased vascular resistance and BP. Numerous foods are abundant in genistein and daidzein such as currants, raisins, hazelnuts, peanuts, coconuts, passion fruit, prunes, as well as many other fruits and nuts.

In two unpublished studies by Pitre et al in SHR, hydrolyzed ion-exchange whey protein isolate (BioZate-1™, Davisco, Eden Prairie, Minnesota) demonstrated significant reductions in mean arterial pressure and heart rate compared to an ion-exchange whey protein isolate. BioZate-1™ at an oral dose of 30 mg/kg, 75 mg/kg, and 150 mg/kg reduced mean arterial pressure by 10 to 18% and HR 10% that was sustained for 24 hours (p < 0.05 for both). The maximum effect was at one to six hours after dosing. These data indicate that the whey protein must be hydrolyzed in order to exhibit an antihypertensive effect, and the maximum BP response is dose dependent.

Bovine casein-derived peptides and whey protein-derived peptides exhibit ACEI activity. These components include B-caseins, B-lg fractions, B2-microglobulin and serum albumin. Whey protein hydrolysates exhibit both in vitro and in vivo ACEI and antihypertensive activity in vivo animal and human studies. The enzymatic hydrolysis of whey protein isolates releases ACEI peptides. The relative in vitro ACEI activity (IC₅₀ – the amount of the substance that causes a 50% inhibition of ACE activity – is 0.45 mg/ml for BioZate-1™. 376 mg/ml for whey protein isolate, compared to 1.3 x 10⁻⁶ for captopril).

Sardine muscle protein, which contains Valyl-Tyrosine (VAL-TYR), significantly lowers BP in hypertensive subjects. Kawasaki et al treated 29 hypertensive subjects with 3 mg of Valyl-Tyrosine sardine muscle concentrated extract for four weeks and lowered BP 9.7 mm Hg/5.3 mm Hg (p < 0.05). Levels of A-I increased as serum A-II and aldosterone decreased indicating that Valyl-Tyrosine is a natural angiotensin converting enzyme inhibitor (ACEI). No adverse effects were noted during the clinical study.

A similar study using a wheat germ hydrolysate, which contains Ile-Valyl-Tyrosine (ILE-VAL-TYR) significantly reduced BP in the SHR model. The mean arterial pressure MAP fell between 10.3 and 19.2 mm Hg after intravenous injection of 5 mg/kg to 50 mg/kg of the wheat germ hydrolysate. This hydrolysate has the natural ACEI (ILE-VAL-TYR), which is also metabolized by aminopeptidase to Valyl-Tyrosine (VAL-TYR), an ACEI.

In addition to ACEI effects, protein intake may also alter catecholamine responses and induce natriuresis. The optimal protein intake, depending on level of activity, renal function, stress and other factors, is about 1.0 to 1.5 gm/kg/day.

### Table 21A

<table>
<thead>
<tr>
<th>FATS and BP</th>
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<tbody>
<tr>
<td></td>
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</tr>
<tr>
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<td>two : ↑ BP</td>
</tr>
<tr>
<td></td>
<td>8 : No change BP</td>
</tr>
<tr>
<td>PUFA :</td>
<td>9 : No change BP</td>
</tr>
<tr>
<td>1 : ↓ BP</td>
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</tr>
<tr>
<td>N-6 PUFA :</td>
<td>1 : ↓ BP</td>
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<td>1 : No change BP</td>
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</tr>
<tr>
<td>N-3 PUFA</td>
<td>1 : ↓ BP</td>
</tr>
<tr>
<td>2 : No change BP</td>
<td></td>
</tr>
<tr>
<td>PUFA/SA Ratio : 5 : No change BP</td>
<td></td>
</tr>
<tr>
<td>MUFAN :</td>
<td>2 : ↓ BP</td>
</tr>
<tr>
<td>5 : No change BP</td>
<td></td>
</tr>
<tr>
<td>SFA :</td>
<td>1 : No change BP</td>
</tr>
</tbody>
</table>

PUFA = Polyunsaturated Fatty Acids  
SFA = Saturated Fatty Acids  
MUFAN = Monounsaturated Fatty Acids
**FATS**

Observational, epidemiologic, biochemical, cross-sectional studies and clinical trials of the effect of fats on BP have been disappointing and inconsistent. However, many of these studies have probably missed small associations, were prone to inaccurate measurement of diet through recall or recording, had inadequate or incorrect BP measurement and did not correct for numerous dietary or nondietary confounding factors. An exhaustive meta-analysis and review of these studies is reported by Morris (Table 21A). In the National Diet Heart Study, there was no change in BP with a polyunsaturated to saturated fat ratio (P/S ratio) in the range of 0.3 to 4.5 in 1,218 subjects over a 52-week study period. The Multiple Risk Factor Intervention Trial (MRFIT) demonstrated that consumption of an extra six grams of trans fatty acids (TFA) per day increased SBP 1.4 mm Hg and DBP 1.0 mm Hg. However, the addition of two grams per day of linolenic acid reduced mean BP by 1.0 mm Hg.

Two large prospective clinical studies, the Nurses Health Study (NHS) and the U.S. Male Study (USMS), showed a neutral effect on BP by all fats studied. In the NHS, 58,218 disease free nurses were evaluated for the incidence of hypertension over a four-year period. A diet questionnaire was used; all confounding factors were controlled during the study. Multivariate analysis showed that the incidence of hypertension was not associated with total fat, saturated fat, and polyunsaturated fat (linoleic acid), or trans fatty acids. Similarly, in the USMS, of 30,681 U.S. male health professionals, which was also a four year study that controlled for confounding factors, the incidence of hypertension was not associated in multivariate analysis by total fat, saturated fat, polyunsaturated fat or trans fatty acids.

However, the type of fat, total daily intake, and relative ratios of fat intake may be more important in determining the BP effect in patients. This is particularly true of the polyunsaturated fats (PUFA) and monounsaturated fats (MUFA), which include omega-3 fatty acids (W-3), omega-6 fatty acids (W-6) and omega-9 fatty acids (W-9) (Table 22 and Table 23). The W-3 FA and W-6 FA are essential fatty acid families, whereas W-9 FA (oleic acid) can be manufactured by the body from the dietary precursor stearic acid.

**OMEGA-3 PUFA (OMEGA-3)**

Alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA) comprise the primary members of the omega-3 PUFA family (Table 23). Omega-3 fatty acids are found in cold water fish (herring, haddock, Atlantic salmon, trout, tuna, cod and mackerel), fish oils, flax, flax seed, flax oil and nuts. Omega-3 PUFA significantly lowers BP in observational, epidemiologic and some small prospective clinical trials. A meta-analysis of 31 studies on the effects of fish oil on BP showed both a dose-related response in hypertension as well as a relationship to the specific concomitant diseases associated with hypertension.

### Table 22

<table>
<thead>
<tr>
<th>Parent Compound</th>
<th>Number of Double Bonds</th>
<th>Family Name</th>
<th>Structural Abbreviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oleic acid</td>
<td>one</td>
<td>Omega-9 (n-9)</td>
<td>18:1n-9 or 18:1n-9</td>
</tr>
<tr>
<td>Palmitoleic acid</td>
<td>one</td>
<td>Omega-7 (n-7)</td>
<td>16:1n-7 or 16:1n-7</td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>two</td>
<td>Omega-6 (n-6)</td>
<td>18:2n-6 or 18:2n-6</td>
</tr>
<tr>
<td>Alpha-linolenic acid</td>
<td>three</td>
<td>Omega-3 (n-3)</td>
<td>18:3n-3 or 18:3n-3</td>
</tr>
</tbody>
</table>

### Table 23

**Metabolic Pathways of the Omega-3 and Omega-6 Fatty Acids**

<table>
<thead>
<tr>
<th>Omega-3 Fatty Acids</th>
<th>Omega-6 Fatty Acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-linolenic acid (ALA)</td>
<td>Linoleic acid (LA)</td>
</tr>
<tr>
<td>18:3n-3</td>
<td>18:2n-6</td>
</tr>
<tr>
<td>Neutrioleic acid</td>
<td>Gamma-linolenic acid (GLA)</td>
</tr>
<tr>
<td>18:4n-3</td>
<td>16:4n-3</td>
</tr>
<tr>
<td>Eicosapentaenoic acid</td>
<td>Dihomo-gammalinolenic acid (DGLA)</td>
</tr>
<tr>
<td>20:5n-3</td>
<td>20:4n-6</td>
</tr>
<tr>
<td>Docosahexanoic acid (DHA)</td>
<td>Arachidonic acid (AA)</td>
</tr>
<tr>
<td>22:6n-3</td>
<td>20:4n-6</td>
</tr>
</tbody>
</table>

At fish oil doses of < 4 gm/day, there was no change in BP in the mildly hypertensive subjects. At 4 to 7 grams of fish oil per day, BP fell 1.6 mm Hg to 2.9 mm Hg and at over 15 grams of fish oil per day, BP decreased 5.8 mm Hg to 8.1 mm Hg. There was no change in BP in the normotensive subjects. However, in those subjects with atherosclerotic disease and hypertension, hyperlipidemia and CHD, BP was reduced as shown below:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mean Fish Oil Dose (gm)</th>
<th>Mean BP Reduction (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>5.6</td>
<td>2.3 – 3.4</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>4.0</td>
<td>4.1</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>4.8</td>
<td>2.9 – 6.3</td>
</tr>
</tbody>
</table>
A study of 399 healthy males showed that a 1% increase in adipose tissue alpha-linolenic acid (ALA) content was associated with a 5 mm Hg decrease in SBP, DBP and MAP.301

Knapp et al demonstrated a significant reduction in BP (p < 0.01) in a group of hypertensive subjects given 15 grams per day of fish oil. Bao et al studied 69 obese, hypertensive subjects in 16 weeks treated with fish oil (3.65 grams omega-3 FA per day), evaluated by 24-hour ambulatory BP monitoring (24 hour ABM). Group I subjects on 3.65 grams per day of omega-3 FA alone reduced 24-hour ABM by 6/3 mm Hg (p < 0.01). Group II subjects who lost an average of 5.6 kg of weight, but received no fish oil, had a 5.5/2.2 mm Hg reduction in BP (p < 0.01). The best BP results were seen in Group III subjects on combined fish oil (omega-3 FA) and weight loss whose BP fell 13.0/9.3 mm Hg and heart rate fell an average of 6 beats/minute.

Mori et al studied 63 hypertensive, hyperlipidemic subjects treated with omega-3 FA, 3.65 grams/day for 16 weeks, and found significant reductions in BP in (p< 0.01), increase HDL2-C (p < 0.0004), decrease in HDL3-C (p < 0.026), decrease in triglycerides (29%), but no change in LDL-C, TC or total HDL-C. Serum glucose and insulin levels also declined.

Studies indicate that docosahexanoic acid (DHA) is very effective in reducing BP and heart rate.376,377 However, formation of EPA and ultimately DHA from ALA in the diet (omega-6 FA), increased dietary saturated fats and trans fatty acids, alcohol and aging through inhibitory effects, or reduced activity of delta-6-desaturase, delta-4-desaturase (Table 23). Eating cold water fish three times per week is as effective as high-dose fish oil in reducing BP in hypertensive patients.14,382 The BP is usually unaffected in healthy non-hypertensive patients.382,388

**OMEGA-6 FATTY ACIDS (OMEGA-6 FA)**

The omega-6 FA family, which includes linoleic acid (LA), gamma-linolenic acid (GLA), dihomo-gamma linolenic acid (DGLA) and arachidonic acid (AA) do not usually lower BP significantly18,239 (Table 23), but may prevent increases in BP induced by saturated fats,288,390 The omega-6 FA are found in flax, flax seed, flax seed oil, conjugated linoleic acid (CLA), canola oil, nuts, evening primrose oil, borage oil and black currant oil. The ideal ratio of omega-3 FA to omega-6 FA is between 2:1 to 4:1 and a polyunsaturated to saturated (P/S) fat ratio greater than 1.5 to 2:1.391 Hydrogenated or partially hydrogenated vegetable oils with trans fatty acids should be avoided as these will increase BP and CHD risk.372 They also have high omega-4 FA concentrations with little or no omega-3 FA.14

GLA and DGLA will enhance synthesis of vasodilating prostaglandins PGE1 and PGI2 preventing the increase in BP by feeding saturated fats.289,390 GLA also completely blocks stress-induced hypertension392,393 due to increased PGE1,394 decreased plasma aldosterone and reduced adrenergic angiotensin II receptor density and affinity.395 Both PGE1 and PGI2 regulate nerve conduction, mental function and neurotransmitter release and action that normalizes stress-induced changes in the hypothalamus and endocrine organs in hypertensive patients given GLA supplementation.289,393,394,395,396 The conversion from LA to GLA and DGLA requires cofactors such as magnesium, potassium, calcium, vitamin B6, vitamin A and beta carotene, vitamin C, niacin, selenium and sodium.289,315,316,317,394

**OMEGA-3 FATTY ACIDS – OTHER CLINICAL EFFECTS**

The omega-3 FA have a multitude of cardiovascular effects whose interplay modulates BP. These include reduction in fibrinogen,381 anti-inflammatory,377 anti-platelet,377 anti-arrhythmic,377,378 hypolipidemic,397 anti-atherosclerotic377 and vasodilatory effects (increases NO levels).377

**OMEGA-3 FA: MECHANISM OF ACTION**

The numerous proposed mechanisms of action of omega-3 FA are outlined in Table 24.182,198,199,200,239,243,244,398-408 Alpha linolenic acid (ALA) competes for the same enzyme as linoleic acid (LA) - i.e. delta-6-desaturase thus reducing arachidonic acid (AA) formation and eicosanoid production of products such as thromboxane A2 (TXa2) (pro-coagulation) and leukotrienes (pro-inflammatory) while increasing production of vasodilatory prostacyclin I (PGI2, and PGU2)239,243,244,289,409 In addition, there is modification of membrane phospholipids, improved membrane fluidity, reduced Ca++ exchange and increased Na+/K+ ATPase activity.243,405,406,407,408 Stimulation of NO production,377 improved insulin sensitivity,182,198,199,200,398,399,400,401,402 and effects on

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**Table 24**182,198,199,200,243,244,379,399,400,402,403,404,406,407,408,

<table>
<thead>
<tr>
<th>Omega-3 and PUFA: Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Stimulates Nitric Oxide (NO)377,398,408 and PGI2 decreases TXa2 and inflammation243,405,406</td>
</tr>
<tr>
<td>- Improves insulin sensitivity and lowers BP</td>
</tr>
<tr>
<td>- N-3 skeletal muscle phospholipid content390</td>
</tr>
<tr>
<td>- Membrane fluidity, membrane phospholipid content182,378,409 regulate gene expression377</td>
</tr>
<tr>
<td>- Mitochondrial uncoupling protein and FA oxidation in liver and skeletal muscle390</td>
</tr>
<tr>
<td>- Thromboxane gene induction (Reduces body fat/increase heat production) energy balance improvement390,398,399</td>
</tr>
<tr>
<td>- Mitochondrial and peroxisomal oxidation in skeletal muscle390</td>
</tr>
<tr>
<td>- Diuretic-like, 5 diuretin uptake, Glycogen storage198,378,399,400,401</td>
</tr>
<tr>
<td>- Improved glucose tolerance377</td>
</tr>
<tr>
<td>- Intradiauricular and inter organ fluid partitioners directing FA away from storage to oxidation,392,400</td>
</tr>
<tr>
<td>- PPARα ligand activators (lipid oxidation)390</td>
</tr>
<tr>
<td>- SREBP-1 suppression (4 lipogenic genes)390</td>
</tr>
<tr>
<td>- Improved Cardiac Function390</td>
</tr>
<tr>
<td>- Improved Endothelial Dysfunction375,379,380,384,404</td>
</tr>
<tr>
<td>- Reduced plasma noradrenaline375</td>
</tr>
<tr>
<td>- Change Calcium Flux390</td>
</tr>
</tbody>
</table>

PPAR = Peroxisome Proliferator activated receptor SREBP-1 = Sterol Response Element- Binding Protein
intracellular and intraorgan fuel partitioning of fatty acids accounts for much of the observed BP-lowering effect.182,399,403

EPA blocks the activity of delta-5-desaturase, which reduces levels of arachidonic acid (AA) and increases DGLA levels and thus PGE1.409 AA is necessary for conversion of EPA to PGI3 and EPA for conversion of DGLA to PGE1 387,409 Dietary caloric restriction will increase the activity of delta-6-desaturase, increasing levels of GLA, DGLA, EPA and DHA as well as PGE1, PGI2 and PGI3.289,317,409,410 The EPA all have ACE inhibitory activity.

A critical and optimal balance of omega-3 and omega-6 essential fatty acids with the nutrition cofactors of minerals, vitamins, antioxidants and electrolytes is important in vasoregulation, thrombosis, BP, vascular health and CVD reduction.

**OMEGA-9 FATTY ACIDS (OMEGA-9 FA)**

Olive oil is rich in monounsaturated fats MUFA (omega-9 FA) (oleic acid), which have been associated with BP and lipid reduction in Mediterranean and other diets.14,18,412 Ferrara et al studied 23 hypertensive subjects in a double-blind, randomized, crossover study for six months comparing MUFA with PUFA.412 Extra virgin olive oil (MUFA) was compared to sunflower oil (PUFA), rich in linoleic acid (W-6 FA). The SBP fell 8 mm Hg (p < 0.05) and the DBP fell 6 mm Hg (p < 0.01) in the MUFA-treated subjects compared to the PUFA-treated subjects. In addition, the need for antihypertensive medications was reduced by 48% in the MUFA group versus 4% in the PUFA (omega-6 FA) group (p < 0.005).

Strazzullo et al found an increase in SBP and DBP in patients when olive oil was replaced with saturated fatty acids.413 Thomsen et al compared 16 hypertensive type II diabetics in a three-week crossover study comparing MUFA (olive oil) with PUFA. There was a significant reduction in clinic BP and 24-hour ABM.414 However, in 47 normotensive healthy subjects given an olive-oil-rich diet versus a PUFA-rich diet, there was a significant reduction in clinic BP and 24-hour ABM.414 However, in 47 normotensive healthy subjects given an olive-oil-rich diet versus a PUFA-rich diet, there was no significant change in BP.415

Olive oil is rich in oleic acid (omega-9 FA). Extra virgin oil has 5 mg of phenols in 10 grams of olive oil, a rich polyphenol antioxidant.412,416 About 4 tablespoons of extra virgin olive oil is equal to 40 grams. The MUFA tend to increase HDL-C more than PUFA417 and the oleate-rich LDL-C is more resistant to oxidation to OXLDL-C.418 The combined antioxidant and antiinflammatory effect of MUFA probably accounts for the BP effects by improved NO bioavailability, reduced ROS, improved endothelial function, vasodilation and inhibition of the OXLDL-stimulation of the angiotensin II receptor (A-II R).26,27,28,29,30,115,116,128,132,138,139

**PALMITOLEIC ACID (POA)**

Palmitoleic acid reduces the incidence of stroke in SHR-stroke prone (SHRSP) without any change in BP.419 This may be due to a direct metabolic improvement in vascular smooth muscle. An extremely low saturated fat intake in the Asian population is associated with an increased risk of intra-cranial hemorrhage (ICH) in women.420 This is also independent of BP. Perhaps some saturated fat and omega-6 FA from dairy products and red meat is essential for membrane integrity and reduction in ICH.

**FIBER**

The clinical trials with various types of fiber to reduce BP have been inconsistent.18,421 Soluble fiber, guar gum, guava, psyllium and oat bran reduce BP and reduce the need for antihypertensive medications in hypertensive subjects, diabetic subjects and hypertensive-diabetic subjects.422,423,424,425 Vuskun et al reduced SBP 9.4 mm Hg in hypertensive subjects with the fiber glucomannan. Keenan gave oat bran (beta glucan) to hypertensive patients and reduced BP 7.5 mm Hg/5.5 mm Hg. The doses required to achieve these BP reductions is approximately 60 grams of oatmeal per day, 40 grams of oat bran (dry weight) per day, 3 grams of beta-glucan per day or 7 grams a day of psyllium.358 In addition, the soluble and insoluble fibers reduce TC, TG, LDL-C and increase HDL.358 The mechanisms for the BP reduction include improved insulin sensitivity,422,426 reduced endothelial dysfunction,422,426 natriuresis and reduced intravascular volume,422,427 decreased sympathetic nervous system activity,422,427 reduced OXLDL,358 and mitigation of postprandial high-fat-meal induced hypertriglyceridemia, hyperglycemia with ED and vasoconstriction.358

**GARLIC**

Good clinical trials utilizing the correct type and dose of garlic have shown consistent reductions in BP in hypertensive patients.14,377,428,429,430,431,432,433,434,435,436,437 Not all garlic preparations are processed similarly and are not comparable in antihypertensive potency.438,439 In addition, cultivated garlic (allium sativum).438,439 wild uncultivated garlic or bear garlic (allium urisinum).438,439,440,441,442,443,444,445,446,447,448 and aged301 or fresh garlic will have variable effects.14,428,429 Mohamadi et al found that wild garlic had the greatest antihypertensive effect in rats, probably mediated through the reduction in A-II levels, increased NO and decreased ROS by the higher content of allicin and other compounds. There is a consistent dose-dependent reduction in BP with garlic mediated through the RAAS and the NO system.439 ALICIN, a synthetic preparation of an active constituent of garlic, lowered BP, insulin and TG to a similar degree as enalapril in the Sprague-Dawley Rat Study by Elkayam et al.449
Table 25

<table>
<thead>
<tr>
<th>Garlic : Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ACEI (Gamma-Glutamyl peptides, flavonolic compounds)</td>
</tr>
<tr>
<td>• Increase NO</td>
</tr>
<tr>
<td>• Decrease sensitivity to NE</td>
</tr>
<tr>
<td>• Increase Adenosine</td>
</tr>
<tr>
<td>• Vasodilation and reduced SVR</td>
</tr>
<tr>
<td>• Inhibit AA metabolites (TxA₂)</td>
</tr>
<tr>
<td>• Reduced aortic stiffness</td>
</tr>
<tr>
<td>• Magnesium (Natural CCB vasodilator)</td>
</tr>
<tr>
<td>• Decreased ROS</td>
</tr>
</tbody>
</table>

compounds with vasodilatory and antioxidant effects, theanine, theobromine, quercetin, epigallocatechin-3-O-gallate (EGCG), gamma-glutamylmethylamide (GMA), tharubigins and theaflavins. Additional studies in humans will be required to accurately assess these BP effects.

MUSHROOMS

The effects of mushrooms on BP in humans has not been studied. However, in the SHR, shiitake and maitake mushrooms reduce BP and serum lipids. Mushrooms are low in carbohydrate, have no sugar, but also have high amounts of zinc and other vitamins and minerals that may reduce BP. In addition, the cellulose provides a small amount of fiber.

SEAWEED

Wakame (Undaria pinnatifida) is the most popular, edible seaweed in Japan. In the SHR, wakame has similar ACEI activity to captopril with similar reductions in BP. In humans, 3.3 grams of dried wakame for four weeks reduced the SBP 14 ± 3 mm Hg and significantly reduced DBP (p < 0.01). In a study of 62 middle-aged, male subjects with mild hypertension given a potassium-loaded, ion-exchanging sodium-adsorbing potassium-releasing seaweed preparation showed significant BP reductions at four weeks on 12 and 24 gm/day of the seaweed (p < 0.01). The MAP fell 11.2 mm Hg (p < 0.001) in the sodium-sensitive subjects and 5.7 mm Hg (p < 0.05) in the sodium-insensitive subjects, which correlated with plasma renin activity (PRA). The urinary sodium excretion decreased, urinary potassium increased and the sodium/potassium urinary excretion ratio decreased indicating that the MAP reduction was dependent on the reduced intestinal absorption of sodium and increased absorption of potassium released from the seaweed preparation. A similar mechanism of BP and stroke reduction was reported in SHR given 10% alginic acid in a seaweed fiber.
Seaweed and sea vegetables contain most all of the seawater's 77 minerals and rare earth elements, fiber and alginate in a colloidal form. However, the concentration of these minerals and alginate are lower than the effective dose needed to reduce BP in most cases. The primary effect of wakame appears to be through its ACEI activity from at least four parent tetrapeptides and possibly their dipeptide and tripeptide metabolites, especially those containing the amino acid sequence TYR-LYS in some combination. Its long-term use in Japan has demonstrated its safety. Other varieties of seaweed may reduce BP by reducing intestinal sodium absorption and increasing intestinal potassium absorption.

**NATURAL ACEI’S**

Many other foods have demonstrated ACEI activity in vitro, but whether they are active after oral ingestion in vivo remains to be proven in human studies (Table 26).

**VITAMIN C**

Vitamin C is a potent water-soluble antioxidant that recycles vitamin E, improves endothelial dysfunction and produces a diuresis. Numerous epidemiologic, observational and clinical studies have demonstrated that the dietary intake of vitamin C or plasma ascorbate concentration in humans is inversely correlated to SBP, DBP and heart rate. Studies in the SHR have shown fairly uniform reductions in BP with vitamin C administration. Long-term epidemiologic and observational follow-up studies in humans also show a reduced risk of CVD, CHD and CVA with increased vitamin C intake. However, controlled intervention trials have been somewhat less consistent or inconclusive as to the relationship of vitamin C and plasma ascorbate levels with BP. Numerous reasons exist for these variable results, including lack of a control group, no baseline BP, small study population, short trial duration, variable vitamin C doses, variable demographics and study population, unknown premorbid vitamin C status or premorbid general vitamin or antioxidant status, concomitant diseases, confounding factors such as smoking, alcohol, weight changes, fiber, etc. were not stated or evaluated, plasma ascorbic acid levels were not measured, the P-value and confidence intervals were not reported, variable BP measurement techniques were employed (clinic or office, home, 24-hour ABM) unknown genetic polymorphisms exist or there was publication bias.

Ness et al published in 1997 a systematic review of MEDLINE-listed peer review journals on hypertension and vitamin C and concluded that if vitamin C has any effect on BP, it is small. However, in the 18 studies that were reviewed worldwide, 10 of 14 showed a significant BP reduction with increased plasma ascorbate levels and 3 of 5 demonstrated a decreased BP with increased dietary vitamin C. In four small, randomized clinical trials of 20 to 57 subjects, one had significant BP reduction, one had no significant BP reduction and two were not interpretable. In two uncontrolled trials, there was a significant reduction in BP.

Koh et al in 1984 evaluated 23 hypertensive women with a BP range of 140-160/90-100 mm Hg over a three month period. Administration of one gram of vitamin C per day reduced office SBP 7 mm Hg (p < 0.05) and DBP 4 mm Hg (p < 0.05). Ceriello et al in 1991 gave IV vitamin C to hypertensive patients with DM and reduced BP significantly.

Trout et al in 1991 gave one gram of vitamin C orally to 12 hypertensive subjects in a randomized crossover study for six weeks. The plasma ascorbate levels increased by 20 umol/liter (p < 0.001), SBP fell 5 mm Hg (p < 0.05) and DBP fell 1 mm Hg (NS).

Duffy et al in 1999 evaluated 39 hypertensive subjects (DBP 90 mm Hg to 110 mm Hg) in a placebo-controlled four-week study. A 2000 mg loading dose of vitamin C was given initially followed by 500 mg per day. The BP was reduced 11 mm Hg (p = 0.03), DBP decreased by 6 mm Hg (p = 0.24) and MAP fell 10 mm Hg (p < 0.02). The plasma ascorbate increased to 49 umol/liter at four weeks (p < 0.001) showing an inverse correlation with MAP and plasma ascorbate levels (p < 0.03). There was no change in cyclic GMP (CGMP), urinary 6 keto-prostaglandin-F1α, or urinary 8 epi-prostaglandin-F2α.

Fotherby et al (2000) studied 40 mild hypertensive and normotensive subjects in a double-blind, randomized, placebo-controlled, crossover study for six months. Men and women age 60 to 80 years (mean age 72 ± 4 years)
were given vitamin C 250 mg twice daily for three months, then crossed over after a one-week washout period. The plasma ascorbate increased to 35 umol/liter (p < 0.001), but clinic BP did not change significantly. However, the 24-hour ABM showed a significant decrease in SBP 2.0 ± 5.2 mm Hg (p < 0.05), but there was no significant change in DBP. However, the higher the BP, the greater the response to vitamin C. Therefore, when the normotensive or borderline hypertensive subjects were excluded, the BP reduction was more pronounced and significant. A significant increase in HDL-C was seen in women (p < 0.007), but not in men. The LDL-C did not change in either group. The conclusion from this study was that vitamin C reduced primarily daytime SBP as measured by 24 hour ABM in hypertensive, but not normotensive subjects. In the hypertensive subjects, SBP was reduced by 3.7 mm Hg ± 4.2 mm Hg (p < 0.05) and DBP fell 1.2 mm Hg ± 3.7 mm Hg (NS).

Block et al (2001) in an elegant depletion-repletion study of vitamin C demonstrated a significant inverse correlation of plasma ascorbate levels, SBP and DBP. During this 17-week controlled diet study of 68 normotensive men aged 39 to 59 years with mean DBP of 73.4 mm Hg and mean SBP of 122.2 mm Hg, vitamin C depletion at 9 mg/day for one month was followed by vitamin C repletion at 117 mg/day repeated twice. All confounders were eliminated, including smoking, exercise, alcohol, weight change and other nutritional intake during the study. Plasma ascorbate was inversely related to DBP (p < 0.0001, correlation -0.48) and to SBP in logistic regression. Persons in the bottom quartile of plasma ascorbate had a DBP 7 mm Hg higher than those in the top quartile. One-fourth of the DBP variance was accounted for by plasma ascorbate alone. Of the other plasma nutrients examined, only ascorbate was significantly and inversely correlated with DBP (p < 0.0001, r = -0.48) for the five week plasma ascorbate levels. Each increase at week five in the plasma ascorbate level was associated with a 2.4 mm Hg lower DBP at week nine.

Hajjar et al evaluated 31 subjects with Stage I hypertension in a double-blind, randomized, placebo, four-week, run-in trial utilizing three doses of vitamin C at 500 mg, 1000 mg, or 2000 mg per day for eight months. The mean age was 62 ± 2 years, 52% male, 90% white with good compliance of 48 ± 2%. The SBP fell significantly by 4.5 ± 1.8 mm Hg (p < 0.05) and DBP fell by 2.8 ± 1.2 mm Hg (p < 0.05) at one month and persisted during the study. No dose response was demonstrated. The BP decrease was not significant, but was lower in the vitamin C group. There was no difference in BP response between the three groups (p = 0.48) and no significant change in serum lipid levels from baseline or between groups although the vitamin C group had an overall trend to improve lipids: TC (p = 0.75), TG (p = 0.87), HDL (p = 0.32) or LDL (p = 0.52).

Ness et al evaluated subjects aged 45-74 in a population based cross sectional analysis and found that an increase in plasma ascorbate of 50 umol/liter reduced BP by 3.6/2.6 mm Hg. Bates et al in a similar cross sectional analysis on 914 elderly patients over 65 years of age confirmed that an increase in plasma ascorbate of 50 umol/liter reduced SBP by 7 mm Hg. In most of the epidemiologic studies, there is a clear inverse relationship between plasma ascorbate levels, dietary intake and BP with a reduction in SBP of 3.6 to 17.8 mm Hg for each 50 umol/liter increase in plasma ascorbate.

In the post hoc analysis in the ADMIT study (Arterial Disease Multiple Intervention Trial), a prospective, double-blind, placebo-controlled study of 363 subjects with PAD (peripheral arterial disease) treated with vitamin C 1000 mg/day, vitamin E 800 IU/day and beta carotene 24 mg/day versus placebo, there was no difference in BP in the normotensive or hypertensive subjects (N = 177). Other studies, however, have shown synergy of combination antioxidants and vitamins in reducing BP, increasing NO, PGE1 and PGI2 levels, and reducing TxA2 levels. The study by Miller et al in 297 elderly patients showed no difference in BP in the treated group given vitamin C, E and beta carotene vs placebo group. However, 87% of all subjects were permitted to take their own multivitamins.

MECHANISM OF VITAMIN C ON BLOOD PRESSURE

Vitamin C improves ED in hypertensive patients with hyperlipidemia and reduces BP in a dose related manner with higher pharmacologic doses. The improvement of ED in hypertensive patients occurs in conduit arteries, epicardial coronary arteries and forearm resistance arteries. Vitamin C restores NO-mediated flow-dependent vasodilation in patients with CHF. Hypertensive patients exhal less NO than healthy patients. Following vitamin C administration, there is an increase in exhaled NO that correlates with BP reduction, especially SBP. Acute oral or intravenous administration

**Table 27**

<table>
<thead>
<tr>
<th><strong>Mechanisms Vitamins C</strong></th>
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</table>
| Reduces ED and improves EDV and lowers BP and SVR in HBP, HLP, CHD, Smokers | Diuresis
| Increase NO and PGI2 | Increase adrenal steroid production
| Improve sympathovagal balance | Decrease cytosolic Ca++
| Antioxidant | Recycles Vit-E, Glutathione, Uric Acid
| Reduces neuropeptide hormones | Reduces thromboxanes and decreases TxA2
| Reduces Lipids | Improves ED in hypertensive and hyperlipidemic patients
| Reduces Leukotrienes | Improves Aortic Collagen, Elasticity and Aortic Compliance
| Increase cGMP and activate VSM K+ channels |
of vitamin C reverses ED and causes acute vasodilation in humans with CHD and in smokers. The multitude of proposed mechanisms for vitamin C in hypertension and other cardiovascular diseases is outlined in Table 27. Grossman et al proposed recently that ascorbic acid modulates the redox state of soluble guanylyl cyclase, activating cGMP-dependent potassium channels that hyperpolarize VSMC-inducing vasodilation.

**VITAMIN C - A PERSPECTIVE**

Combined nutrients, vitamins, minerals, and antioxidants have clearly been shown to lower BP in DASH-I, DASH-II, NHANES-III, Vanguard, and other studies. Although these varied diets confer more anti-hypertensive and cardiovascular benefits than any single nutrient, it is also quite probable that vitamin C as a single nutrient plays a significant role in the regulation of BP in both normotensive and hypertensive patients. Almost all studies and reviews reported have shown an inverse relationship to vitamin C intake and plasma ascorbate levels that is reasonably consistent among different study groups, populations and the variable study designs. Hypertensive subjects were found to have significantly lower plasma ascorbate levels compared to normotensive subjects (40 umol/liter vs 57 umol/liter respectively). Evidence supports the fact that plasma ascorbate is inversely correlated with BP even in healthy normotensive individuals. The NHANES-II Study found 20% of U.S. males have plasma ascorbate levels below 27 umol/liter and 30% of U.S. black males were below 27 umol/liter. This could partially account for the higher prevalence of hypertension in blacks.

Pharmacokinetic studies have documented the existence of at least three or more ascorbate compartments of which plasma is only one. Human organs such as adrenal, pituitary, liver, spleen, pancreas, brain, and lens of the eye actively concentrate ascorbate against a concentration gradient and achieve levels 20-to 100-fold greater than plasma. It is possible that during vitamin C deprivation, these organs gain relative priority over the vascular system and other organs as to ascorbate concentrations. The body stores of vitamin C then may be more relevant than plasma levels as it correlates with BP. This vascular tissue-organ depletion theory is consistent with many of the proposed mechanisms of vitamin C shown in Table 27. Vitamin C is not pro-oxidant and, in fact, significantly reduces oxidative stress as measured by the ratio of urinary 8-oxoguanine to 8-oxoadenine.

**SUMMARY AND CONCLUSIONS VITAMIN C AND BLOOD PRESSURE**

The present conclusions based on these available studies correlating vitamin C and BP are shown in Table 28. The observational, epidemiologic and prospective clinical trials point strongly to a role of vitamin C in reducing BP in hypertensive subjects and normotensive subjects as well as those in other disease categories. A dose relationship is suggested, but the efficacy of “supraphysiologic” doses of vitamin C and BP effects are yet to be confirmed. More sound clinical trials are welcomed and needed.

**VITAMIN E**

The relationship of vitamin E and BP has been studied in vitro, extensively in animals (SHR), but limited studies have been done in humans. Alpha tocopherol inhibits thrombin-induced endothelin secretion in vitro at least partially through protein kinase C (PKC) inhibition. Reduced PKC levels reduce vascular smooth muscle (VSM) proliferation through inhibition of activated protein-1 (AP-1) and nuclear factor kappa-B (NFkB). This, in turn, improves ED, lowers SVR and reduces BP.

Newaz et al gave gamma-tocotrienol 15 mg/kg to SHR and found significant reductions in lipid peroxides in plasma and in blood vessel walls, increased superoxide dismutase (SOD) activity, increased total antioxidant status (TAS) and lowered BP (p < 0.001). In a similar study, Newaz et al gave 34 mg/kg of alpha-tocopherol to SHR and WKY rats. Lipid peroxide levels were decreased in plasma and in vascular walls, plasma SOD activity increased, TAS increased and BP fell (p < 0.001). In a follow-up, dose response study, Newaz administered alphatocopherol to SHR in doses of 17 mg/kg, 34 mg/kg or 170 mg/kg. Nitric oxide synthase (NOS) increased significantly (p < 0.01) only at the 34 mg/kg dose and BP fell the most at the 34 mg/kg dose (p < 0.001).
Other animal studies have shown beneficial results of alpha-tocopherol on hypertension and stroke in the SHR.541,542 Improved membrane fluidity and BP in SHR and WKY rats542 and prostacyclin production, serum lipids and BP using a mixture of alpha-tocopherol and tocotrienols.543

Human studies of vitamin E in doses of 400 to 1000 IU/day, although limited, have shown beneficial effects on improving insulin sensitivity,544 lowering serum glucose,544 inhibiting TXA2,529 increasing serum glutathione levels,544 increasing intracellular magnesium,544 improving arterial compliance (37 to 44%) (independent of arterial pressure),547 reducing ED and vascular resistance547,548 and decreasing OXLDL.548 However, reductions in BP in hypertensive subjects have been inconsistent, limited to small numbers of subjects, or it has been difficult to interpret the results for a variety of reasons.544,545,549

Barbagallo et al544 evaluated 24 hypertensive subjects in a double-blind, randomized, placebo-controlled study who received vitamin E 600 IU/day for four weeks. The BP in both treatment and placebo groups was decreased significantly (p < 0.001 for SBP and p < 0.005 for DBP), but both groups received furosemide 25 mg per day. The effects of vitamin E on BP cannot be interpreted in this study.

Palumbo et al545 administered 300 IU vitamin E per day to 142 treated hypertensive subjects in a randomized, open-labeled trial for 12 weeks. Clinic and 24 hour ABM showed no change in SBP and a small decrease in 24-hour ABM, DBP of –1.6 mm Hg (95% confidence intervals –2.8 to 0.4 mm Hg at p = 0.06). However, the mean BP at entry was 147/88 mm Hg in the vitamin E group, indicating reasonably good BP control by JNC-VI criteria. The day and night changes in mean ABM were not significant. The antihypertensive treatment clearly restricted the possibility of actually measuring a BP-lowering effect of vitamin E.

Lino et al549 performed a double-blind, placebo-controlled study of the effects of dl-alpha-tocopherol nicotinate in 94 hypertensive subjects with cerebral atherosclerosis. Subjects received 3000 mg of the study vitamin for four to six weeks. In subjects with hypertension, the SBP declined from 151.0 ± 22.1 mm Hg to 139.2 ± 16.8 mm Hg (p < 0.05), but DBP did not change.

If vitamin E has an antihypertensive effect, it is probably small and may be limited to untreated hypertensive patients or those with known vascular disease or other concomitant problems such as diabetes or hyperlipidemia.547,548,549 However, vitamin E does improve ED through numerous mechanisms that could improve vascular health, reduce vascular and target organ damage that is BP-dependent or independent546,550 (Figure 23). Hypertensive patients, compared to normotensive patients, have significantly lower plasma and cell content of vitamins E and C with increased lipid peroxidation.550

VITAMIN D

Epidemiological, clinical and experimental investigations all demonstrate a relationship between the plasma levels of 1,25 (OH)2 D3 (1,25-dihydroxycholecalciferol), the active form of vitamin D and BP.551,552,553,554,555,556,557 This includes a vitamin-D-mediated reduction in BP in hypertensive patients. Although the mechanism of action of vitamin D on vascular tone and BP is not completely understood, both a direct effect on cell membranes and an indirect effect on calcium transport, metabolism and excretion have been shown.551

It has been difficult to dissociate the effects of calcium from vitamin D on BP in humans. Numerous studies have verified the finding of an inverse relationship between dietary calcium intake and BP.558 This relationship applies to all ages, gender, racial, and socioeconomic groups.551 A low serum ionized calcium level is particularly common in salt-sensitive, low-renin, hypertensive patients who have increased intracellular calcium concentration in platelets, lymphocytes and renal proximal tubular cells.551,558,559,560

Vitamin D may have an independent and direct role in the regulation of BP551,552,553 and insulin metabolism.552,553 A study of 34 middle-aged men demonstrated that serum levels of 1,25 (OH)2 D3 were inversely correlated to BP (p < 0.02), VLDL triglycerides (p < 0.005) and to triglyceride removal after intravenous fat tolerance test (p < 0.05).552 Serum levels of 25 (OH)2 D3 were correlated to fasting insulin (p < 0.05), insulin sensitivity during clamp (p < 0.001) and lipoprotein lipase activity in adipose tissue (p < 0.005) and skeletal muscle (p < 0.03).552 Holdaway et al552 found no difference in 25 (OH)2 D3 levels in a group of hypertensive versus normotensive subjects.561 The Tromso Study analyzed calcium and vitamin intake in 7,543 men and 8,053 women and found a significant linear decrease in SBP and DBP with increasing dietary calcium intake in both sexes (p < 0.05); however, vitamin D intake had no significant effect on BP.562

In the deoxycorticosterone acetate salt model of hypertension, dietary manipulation of vitamin D has been shown to reduce BP without a change in calcium levels, indicating a direct effect on BP regulation.551,563,564 Vascular tissue contains receptors for both calcium-regulating hormones PTH and 1,25 (OH)2 D3.564 MacCarthy demonstrated that 1,25 (OH)2 D3 antagonizes the mitogenic effect of epidermal growth factor on proliferation of vascular smooth muscle cells.565

Lind, in double-blind, placebo-controlled studies, found that BP was lowered with vitamin D during long-term treatment of patients with intermittent hypercalcemia.554,555 In another study, Lind et al demonstrated that total and ionized calcium levels were increased, but DBP was significantly decreased, and the hypotensive effect of vitamin D was statistically significant.555
was inversely related to the pretreatment serum levels of 1,25 (OH)₂ D₃ and additive to antihypertensive medications. Pfeifer et al showed that short-term supplementation with vitamin D₃ and calcium is more effective in reducing SBP than calcium alone. In a group of 148 women with low 25 (OH)₂ D₃ levels, the administration of 1200 mg calcium plus 800 IU of vitamin D₃ reduced SBP 9.3% more (p < 0.02) than did 1200 mg of calcium alone. The HR fell 5.4% (p = 0.02), but DBP was not changed.

VITAMIN B-6 (PYRIDOXINE)

Low serum vitamin B₆ levels are associated with hypertension in rats and humans. Vitamin B₆ is a readily metabolized and excreted water soluble vitamin. Six different B₆ vitamins exist, but pyridoxal 5' phosphate (PLP) is the primary and most potent active form that is produced by rapid hepatic oxidation by pyridoxine phosphate oxidase and pyridoxine kinase in the presence of zinc and manganism. Numerous PLP-dependent enzymes exist that are involved in metabolic pathways that include carbohydrate metabolism, sphingolipid biosynthesis and degradation, amino acid metabolism, heme biosynthesis and hormone and neurotransmitter biosynthesis such as steroid hormones, thyroid hormone, gamma amino butyric acid (GABA), histamine, norepinephrine (NE) and serotonin. Vitamin B₆'s participation in neurotransmitter and hormone biosynthesis, amino acid reactions with kynureninase, cystathionine synthetase, cystathionase and membrane L-type calcium channels account for much of its antihypertensive effects. Vitamin B₆ (PLP) is involved in the transsulfuration pathway of homocysteine metabolism to cysteine.

Animal studies in specific rat strains have demonstrated an increase in BP, NE and epinephrine plasma levels, increase in the NE cardiac turnover, reduced CNS brainstem NE, GABA and serotonin content that completely reverses after vitamin B₆ repletion. Pyridoxine at 10 mg/kg in B₆-deficient rats (B₆DHT) reduced BP from 143 mm Hg to 119 mm Hg within 24 hours (p < 0.05). In these B₆DHT rats, PLP enhanced binding of CCB’s to the vascular membrane indicating that PLP corrects membrane abnormalities and is an endogenous modulator of DHP-sensitive (dihydropyridine-sensitive) calcium channels. Low calcium levels and low B₆ levels potentiate BP increases in rats, whereas replacement of both will reduce BP. Vitamin B₆ plus tryptophan reduced BP more than monotherapy with each in rats, probably related to effects on brain stem serotonin and kynurenine. There is a structural similarity of the B₆ vitamins to the DHP-CCB’s, and CCB’s are most effective in B₆ deficient rats.

Supplemental vitamin B₆ in the diets of prehypertensive, obese, Zucker and sucrose-induced hypertensive rats, and SHR reduces BP by increasing the synthesis of cysteine from methionine. Cysteine acts directly on aldehydes and neutralizes their effects. Aldehydes bind sulfhydryl groups of membrane proteins and alter calcium channels (L-type), which increase cytosolic free calcium, cause VSM constriction and elevate BP. Aldehydes also induce hyperglycemia and promote insulin resistance. Cysteine is also a precursor of glutathione, which neutralizes aldehydes and further improves BP and glucose metabolism. Thus, vitamin B₆ reduces both movement of calcium into cells (cytosolic Ca++) and decreases intracellular sarcoplasmic reticulum release of calcium.

One human study by Aybak et al proved that high dose vitamin B₆ significantly lowered BP. This study compared 9 normotensive men and women with 20 hypertensive subjects, all of whom had significantly higher BP, plasma NE and HR compared to control normotensive subjects. Subjects received 5 mg/kg/day of vitamin B₆ for four weeks. The SBP fell from 167 ± 13 mm Hg to 153 ± 15 mm Hg, an 8.4% reduction (p < 0.01) and the DBP fell from 108 ± 8.2 mm Hg to 98 ± 8.8 mm Hg, a 9.3% reduction (p < 0.005). Plasma NE was reduced from 1.80 ± .21 nmol/l to 1.48 ± .32 nmol/l (18% reduction, p < 0.005); plasma epinephrine fell from 330 ± 46 pmol/l to 276 ± 67 pmol/l (16% reduction, p < 0.05). There was no significant change in heart rate.

The proposed mechanisms of hypertension in vitamin B₆ deficient animals and humans include:

1. Central nervous system, and brain stem depletion of neurotransmitters such as NE, serotonin and GABA, which lead to an increase in sympathetic outflow.
2. Increased peripheral SNS activity.
3. Increased VSMC calcium uptake and increased intracellular calcium release.
4. Increased end-organ responsiveness to glucocorticoids and mineralocorticoids (aldosterone).
5. Increased aldehyde levels.
6. Insulin resistance.

In summary, vitamin B₆ has multiple antihypertensive effects that resemble those of central alpha agonists (i.e. clonidine), calcium channel blockers (i.e. DHP-CCB like amlodipine) and diuretics. Finally, changes in insulin sensitivity and carbohydrate metabolism may lower BP in selected hypertensive individuals with the metabolic syndrome of insulin resistance. Chronic intake of vitamin B₆ at 200 mg per day is safe and has no adverse effects. Even doses up to 500 mg per day are probably safe.
FLAVONOIDS

Over 4,000 naturally occurring flavonoids have been identified in such diverse substances as fruits, vegetables, red wine, tea, soy and licorice. Flavonoids (flavonols, flavones and isoflavones) are potent free radical scavengers that inhibit lipid peroxidation, prevent atherosclerosis, promote vascular relaxation and have antihypertensive properties. In addition, they reduce stroke, and provide cardioprotective effects that reduce CHD morbidity and mortality in the Zutphen Elderly Study, Finnish Study and U.S. Health Professionals Study. Various flavonoids have undergone extensive scientific studies that demonstrate a wide variety of protective cardiovascular effects. Soy, which contains diadzein and genistein, lowers total cholesterol, low density lipoprotein cholesterol (LDL-C), BP and reduces coronary and generalized thrombosis. Red wine contains quercetin, which reduces oxidation of LDL, decreases platelet aggregation. Blueberries (vaccinium myrtillus) are rich in antioxidants, reduce oxidized LDL and are more potent than vitamin C on a molar basis as an antioxidant. Licorice root (glycyrrhiza glabra) is a potent antioxidant, anti-inflammatory, antiplatelet and anti-viral, but it may lower potassium, increase sodium retention and elevate BP due to a mineralocorticoid action when used in high doses.

Very few studies have been done in hypertensive humans to determine the effects of flavonoids on BP. Hodgson et al studied 59 subjects with high normal SBP (SBP ≥ 125 mm Hg) in a randomized, double-blind, placebo-controlled two-way parallel design for eight weeks. The treatment group received one capsule daily containing 55 mg of isoflavonoids from a soy product with 30 mg genistein, 16 mg biochanin A, 1 mg daidzein and 8 mg formononetin. The clinic and 24-hour ABM showed no significant change in BP. This study has many limitations; it was not a true hypertensive population, so effects on BP would be minimal at best, it was limited to a soy product extract with limited number and combinations of isoflavonoids, and the dose administered may have been too small.

Genistein and diadzein inhibit tyrosine kinase activity, which decreases vascular smooth muscle contraction (VSMC), lowers BP and inhibits oxidation activity in the blood vessel. However, Hodgson et al were unable to demonstrate any reduction in urinary F-2 isoprostanes in human subjects with high normal BP given a 55 mg daily isoflavonoid supplement for eight weeks. Urinary F-2 isoprostanes are the best available marker for in vivo lipid peroxidation.

Asgary et al evaluated the flavonoid rich plant, achillea wilhelmsi, in a group of 120 hypertensive, hypercholesterolemic men and women for six months. Significant reductions in TC, LDL, TG, and increased HDL as well as significant reductions in SBP and DBP were found (p<0.05).

Dietary flavonoids may reduce CVA, CHD, and MI independent of any effect on BP. Additional studies are needed to determine the type and amount of dietary flavonoids required to produce significant effects on BP.

LYCOPENE (CAROTENOID)

Lycopene is a non-provitamin-A carotenoid, potent antioxidant found in tomatoes and tomato products, guava, pink grapefruit, watermelon, apricots, and papaya in high concentrations. Lycopene has recently been shown to produce a significant reduction in BP, serum lipids and oxidative stress markers. Paran et al evaluated 30 subjects with Grade I hypertension, age 40-65, taking no antihypertensive or antilipid medications treated with a tomato lycopene extract for eight weeks. The SBP was reduced from 144 to 135 mm Hg (9 mm Hg reduction, p < 0.01) and DBP fell from 91 to 84 mm Hg (7 mm Hg reduction, p < 0.01). A similar study of 35 subjects with Grade I hypertension showed similar results on SBP, but not DBP. Serum lipids were significantly improved in both studies without change in serum homocysteine.

COENZYME Q-10 (UBIQUINONE)

Coenzyme Q10 (CoQ10) is a potent lipid phase antioxidant, free radical scavenger, co-factor and coenzyme in mitochondrial energy production and oxidative phosphorylation that regenerates vitamins E, C, and A, inhibits oxidation of LDL, membrane phospholipids, DNA, mitochondrial proteins, lipids, reduces TC, and TG, raises HDL-C, improves insulin sensitivity, reduces fasting, random and postprandial glucose, lowers SVR, lowers BP and protects the myocardium from ischemic reperfusion injury. CoQ10 improves mitochondrial energy production, enhancing myocardial infusion with improved diastolic function, left ventricle (LV) function, Left ventricle wall tension (LVWT) and NYHA (New York Heart Association) class for CHF.

Serum levels of CoQ10 decrease with age and are lower in patients with diseases characterized by oxidative stress such as hypertension, CHD, hyperlipidemia, DM, atherosclerosis, and in those who are involved in aerobic training, patients on total parenteral nutrition (TPN), those with hyperthyroidism and patients who take statin drugs. Enzymatic assays showed a deficiency of CoQ10 in 39% of 59 patients with essential hypertension versus only 6% deficiency in controls (p < 0.01). There is a high correlation of CoQ10 deficiency and hypertension. Most foods contain minimal CoQ10, which is primarily found in meat and seafood. Supplements are needed to maintain normal serum levels in many of these disease states and in some patients taking statin drugs for hyperlipidemia.
Numerous animal studies in SHR, uninephrectomized rats treated with saline or deoxycortisone and in experimentally-induced hypertension in dogs, have demonstrated significant reductions in BP following oral administration of \( \text{CoQ}_{10} \) at doses of 60 mg per day or more.\(^{609,610,611,612} \)

Human studies have also demonstrated significant and consistent reductions in BP in hypertensive subjects following oral administration of 100 mg to 225 mg per day of \( \text{CoQ}_{10} \). Digiesi et al.\(^{608} \) studied 26 hypertensive subjects with an average BP of 164.5/98.1 mm Hg given \( \text{Co-Q-10} \), 50 mg oral bid for 10 weeks. The SBP fell from 164.5 mm Hg to 146.7 mm Hg, an 11% reduction (\( p < 0.001 \)). The DBP was reduced from 98.1 mm Hg to 86.1 mm Hg, a 12% reduction (\( p < 0.001 \)). The \( \text{CoQ}_{10} \) serum levels increased by .97 \( \mu \text{g/ml} \) (\( p < 0.02 \)), which was highly correlated with the BP reduction. In addition, the 24-hour ABM showed significant reductions in SBP and DBP of 18 mm Hg and 10 mm Hg respectively (\( p < 0.001 \)). The TC fell 10 mg% (\( p < 0.005 \)), HDL rose 2 mg% (\( p < 0.01 \)) and SVR fell 29% (\( p < 0.02 \)). There was no significant change in plasma renin activity (PRA), serum K\(^+\), serum Na\(^+\), urinary K\(^+\) or Na\(^+\) or urine aldosterone. Finally, the serum endothelin level, EKG, and echo were not significantly different.

Langsjoen et al.\(^{397} \) placed 109 hypertensive subjects taking antihypertensive medications on 225 mg per day of \( \text{CoQ}_{10} \) for four months and demonstrated significant reductions in mean SBP from 159 to 147 mm Hg, a reduction of 12 mm Hg (\( p < 0.001 \)) and mean DBP from 94 mm Hg to 85 mm Hg, a reduction of 9 mm Hg (\( p < 0.001 \)). Serum \( \text{CoQ}_{10} \) levels were adjusted to an average of 3.02 \( \mu \text{g/ml} \), but all subjects had levels therapeutic at > 2.0 \( \mu \text{g/ml} \). The \( \text{CoQ-10} \) dose varied from 75 to 360 mg/day. There was improvement in diastolic LV function, LVWT, LVH and NYHA class (\( p < 0.001 \)), thought to be mediated secondary to a neuroendocrine response with reduction in catecholamines and a fall in BP. In addition, improved bioenergetics were noted with improved adrenal function and vascular endothelial function.\(^{613} \) About 51% of subjects were able to discontinue between one to three antihypertensive drugs (37% stopped one drug, 11% stopped two drugs, 4% stopped three drugs) at an average of 4.4 months after \( \text{CoQ-10} \). No side effects were noted. The reduction in drug use by category was 16.7% decrease in digitalis, 40% decrease in diuretics, 59% decrease in beta blockers, 27.5% decrease in calcium channel blockers, 31.7% decrease in angiotensin-converting enzyme inhibitors, and a 35% decrease in other antihypertensive drugs.\(^{397} \)

Yamagami et al.\(^{614} \) observed a \( \text{CoQ}_{10} \) deficiency in 29 subjects with essential hypertension and found significant improvement in their BP and correction of the \( \text{Co-Q-10} \) deficiency following oral intake of 1-2 mg/kg/day. Tsuyuaki et al.\(^{615} \) found that \( \text{CoQ}_{10} \) at 30 mg/day when added to a beta blocker, reduced the negative inotropic effect and lowered BP. Richardson et al.\(^{616} \) demonstrated a significant reduction in systolic and diastolic blood pressure in 16 subjects with essential hypertension on 60 mg/day of \( \text{CoQ}_{10} \) treatment for 12 weeks as well as normalization of their cardiac output. Hamada et al.\(^{617} \) did not see a significant change in BP in 12 hypertensive subjects treated with \( \text{CoQ}_{10} \) at 60 mg/day for four weeks, but the negative inotropic effect of a beta blocker was reduced, and the malaise and fatigue in the patients improved. Yamagami et al.\(^{613} \) showed a significant decrease in SBP in 20 essential hypertensive subjects with low \( \text{CoQ}_{10} \) levels (less than 0.9 \( \mu \text{g/ml} \)) who were randomized to receive either placebo or \( \text{CoQ}_{10} \) at 100 mg/day for 12 weeks. The BP decreased significantly in the \( \text{CoQ}_{10} \) group between 8-12 weeks. Montaldo et al.\(^{618} \) studied 15 hypertensive subjects on 100 mg/day of \( \text{Co-Q-10} \) for 12 weeks and noted a significant reduction in BP at rest and exercise as well as a significant improvement in myocardial stroke work index.

Digiesi et al.\(^{607} \) in 1992 evaluated 10 subjects with essential hypertension treated with oral \( \text{CoQ}_{10} \), 50 mg BID for 10 weeks. The SBP fell from 161.5 ± 5.1 mm Hg to 142.2 ± 5.3 mm Hg (\( p < 0.001 \)) and the DBP fell from 98.5 ± 1.7 mm Hg to 83.1 ± 2.0 mm Hg (\( p < 0.001 \)). Plasma \( \text{CoQ}_{10} \) levels increased from 0.69 ± 0.1 \( \mu \text{g/ml} \) to 1.95 ± 0.3 \( \mu \text{g/ml} \) (\( p < 0.02 \)). In addition, TC decreased from 227 ± 24 mg% to 203.7 ± 20.6 mg% (\( p < 0.01 \)) and serum HDL cholesterol increased from 42 ± 3.0 mg% to 45.9 ± 3.0 mg% (\( p < 0.01 \)). The PRA, urine K\(^+\), Na\(^+\) and aldosterone did not change. The SVR decreased significantly and correlated directly with BP reduction.

Digiesi et al.\(^{1990} \) evaluated 18 subjects with essential hypertension, off all antihypertensive drugs, treated with \( \text{CoQ}_{10} \), 100 mg orally per day for 10 weeks versus a vitamin B complex. The \( \text{CoQ10} \) treatment for 12 weeks. The SBP fell from 161.5 ± 5.1 mm Hg to 152 ± 4.6 mm Hg (\( p < 0.05 \)) and a DBP reduction from 106 ± 4.6 mm Hg to 97 ± 4.1 mm Hg.
(9 mm Hg reduction, p < 0.05). In addition, the heart rate fell from 112 ± 7.8 to 85 ± 4.8 per minute (p < 0.05). Fasting and two hour insulin fell 45% and 35% respectively (p < 0.05), as fasting glucose decreased 33% (p < 0.05). Serum TG fell 10% and HDL-cholesterol increased significantly (p < 0.05), lipid peroxides decreased (p < 0.05), malondialdehyde fell (p < 0.05) and oleic conjugates were reduced (p < 0.05). Serum vitamin A, C, E and beta carotene levels increased. The only changes in the B-vitamin complex group were increases in vitamin C and beta carotene (p < 0.05).

The mechanism of action of CoQ10 includes a reduction in SVR, decreased degradation of membrane phospholipids, decreased membrane phospholipase A2 activity, membrane stabilizing activity, decreased catecholamine and aldosterone levels, improved insulin sensitivity, decreased OxLDL, antioxidant effects on endothelium and vascular smooth muscle (VSM) with increased NO, decreased VSM hypertrophy, vasodilation, decreased ED and improved mitochondrial energy production with less vascular ischemia.377,602,603,607

In summary, CoQ10 has consistent and significant anti-hypertensive effects in patients with essential hypertension. The major conclusions from in vitro, animal and human clinical trials indicate the following:
1. Compared to normotensive patients, essential hypertensive patients have a high incidence of CoQ10 deficiency documented by serum levels. Doses of 120 to 225 mg per day of CoQ10, depending on the delivery method and concomitant ingestion with a fatty meal, are necessary to achieve a therapeutic level of over 2 ug/ml. This is usually 1-2 mg/kg/day of CoQ10. The best studied and most bioavailable CoQ10 supplement is Q-Gel, (Tishcon Corp, Westbury, New York). Use of this special delivery system allows better absorption and lower oral doses.

3. Patients with the lowest CoQ10 serum levels may have the best antihypertensive response to supplementation.
4. The average reduction in BP is about 15/10 mm Hg based on reported studies.
5. The antihypertensive effect takes time to reach its peak level, usually at about four weeks, then BP remains stable. The antihypertensive effect is gone within two weeks after discontinuation of CoQ10.
6. Approximately 50% of patients on antihypertensive drugs may be able to stop between one and three agents. Both total dose and frequency of administration may be reduced.
7. Even high doses of CoQ10 have no acute or chronic adverse effects.

Other favorable effects on cardiovascular risk factors include improvement in the serum lipid profile and carbohydrate metabolism with reduced glucose and improved insulin sensitivity, reduced oxidative stress, reduced heart rate, improved myocardial LV function and oxygen delivery and decreased catecholamine levels.

**ALPHA LIPOIC ACID (ALA)**

Alpha lipoic acid (ALA) is a potent and unique thiol compound-antioxidant that is both water and lipid soluble.377 Alpha lipoic acid helps to recirculate tissue and blood levels of vitamins and antioxidants in both lipid and water compartments such as vitamin C and vitamin E, glutathione, and cysteine.377,619,620 To date, only animal studies in the SHR have been performed to determine the effects of ALA on the vasculature and BP.377,619,621 Vasdev et al.619 administered 500 mg/kg/day in their feed, which was equivalent to 26 mg/kg body weight of ALA to the SHR for nine weeks. There was a significant decrease in SBP (p < 0.001), as well as reduction in cytosolic and platelet, calcium, glucose, insulin levels, tissue aldehyde conjugates in the liver, kidney and aorta. Most important, there was evidence of structural improvement in the vasculature with reduced vascular damage, hypertensive VSMH and atherosclerotic changes. The reduction in SBP in the ALA-treated SHR was from a mean of 180 mm Hg to 140 mm Hg (p < 0.001); whereas the untreated SHR had an increase in SBP from a baseline of 180 mm Hg to 195 mm Hg over the nine-week study period. The decrease in BP was gradual and did not show a further decrease after five weeks of ALA treatment.

The vascular changes in the kidneys of the untreated SHR showed hyperplasia of the smooth muscle, thickening and narrowing of the lumina of the small arteries and arterioles, vacuoles and PAS-positive material in the walls of the arteries. On the other hand, the ALA-treated SHR kidneys had minimal smooth muscle cell hyperplasia, minimal thickening of the wall and no narrowing of the lumina in the small arteries and arterioles. Thus, ALA attenuated the renal vascular hyperplasia in the SHR. In this study of the SHR, ALA reduced blood pressure, biochemical and histologic changes. The dose that would be required for an average 70 kg human patient would be about 2,000 mg per day of ALA. However, it should be emphasized that no dose response study in human hypertension has been done to date.

The mechanisms by which ALA reduces BP and promotes improvement in vascular function and structure are numerous.619,620,622-632 It is known that endogenous aldehydes bind sulphydryl groups (SH) in membrane proteins that alter membrane calcium channels (especially L-type calcium channels), which increase cytosolic free calcium, increase vascular tone, SVR and BP.619 Thiol compounds, such as ALA and N-acetyl cysteine (NAC), bind these endogenous aldehydes, normalize the membrane calcium channels and decrease cytosolic free calcium. In addition,
ALA increases levels of glutathione and cysteine, which bind aldehydes and increase their excretion, and increase antioxidant-vitamin levels of ascorbic acid and vitamin E, which improve endothelial dysfunction. ALA acts like a calcium channel blocker (CCB) through these indirect mechanisms (Figure 24 and Figure 25). A detailed summary of the mechanism of action of ALA is shown in Table 29. Glutathione, which supplies 90% of nonprotein thiols in the body, is depleted in SHR and human hypertension; thus, ALA by increasing levels significantly, reducing aldehydes and closing L-type calcium channels in cell membranes may reduce vascular tone, SVR and BP.625,626,627,628,629

**N-ACETYL CYSTEINE (NAC)**

N-acetyl cysteine (NAC), a source of sulfhydryl groups, is a potent thiol compound and antioxidant that scavenges radical oxygen species (ROS) and supports intracellular glutathione synthesis by binding to endogenous aldehydes, reducing their production and increasing excretion to non-toxic compounds. N-acetyl cysteine also increases interleukin 1-B (IL-1B)-induced nitrite production by increasing (Nitric Oxide Synthase - messenger RNA) transcription and protein expression, elevating NO levels, reducing SVR and BP. These antihypertensive effects of NAC have been shown in SHR, but no human hypertensive studies have been published to date. Similar to ALA, NAC improves the L-type calcium channel in cell membranes, which decreases cytosolic calcium, SVR and BP through aldehyde binding.634,635,636,637

N-acetyl cysteine in doses of 600 mg per day improved capillary blood flow velocity in smokers through its antioxidant effect by improving glutathione levels, reducing ROS, increasing NO, decreasing peroxynitrate and improving ED.638 Furthermore, NAC lowers homocysteine639,640,641,642 and lipoprotein (a).639 and potentiates nitroglycerin-mediat-
ed vasodilation\textsuperscript{643} and reversal of platelet aggregation.\textsuperscript{644} All of these effects may have beneficial effects on the vascular system and BP. N-acetyl cysteine, like ALA, magnesium, vitamin B\textsubscript{6}, vitamin C and possibly vitamin E, have natural calcium channel blocking activity (Table 30).

Cabassi \textit{et al}\textsuperscript{645} have recently shown that NAC treatment in the SHR improves SBP, HR, aortic endothelial function, peroxynitrite-induced impairment of endothelial-independent relaxation, aortic oxidized/reduced glutathione balance (GSSG/GSH), malondialdehyde (MDA) content and 3-nitrotyrosine (3-NT). NAC may have both an anti-hypertensive effect as well as a protective effect against aortic vascular dysfunction.\textsuperscript{545}

L-ARGININE

L-arginine is the primary precursor for the production of nitric oxide (NO)\textsuperscript{646,647} (Figures 6, 7 and 11), which has numerous cardiovascular effects\textsuperscript{57,535,647} (Table 6), mediated through conversion of L-arginine to NO by eNOS to increase cyclic GMP levels in VSM, improve ED and reduce vascular tone and BP.\textsuperscript{648} Patients with hypertension, hyperlipidemia and atherosclerosis have elevated serum levels of ADMA, which activates NO.\textsuperscript{535,649} Administration of L-arginine in humans at doses of 10 grams per day will increase coronary artery blood flow, reduce angina and improve peripheral blood flow and peripheral vascular disease symptoms.\textsuperscript{535,650,651,652}

Hypertension induced by NACL loading in the Dahl sensitive rats,\textsuperscript{653,654,655} in adrenocorticotrophin (ACTH)-induced hypertension in the Sprague-Dawley rats\textsuperscript{656} and in the SHR (spontaneously hypertensive rats) can be prevented and partially reversed by chronic and acute dietary L-Arginine supplementation. L-Arginine reduced BP, SVR, LV mass, collagen content, improved coronary hemodynamics and restored plasma Nox (nitrite/nitrate) and c-Jun N-terminal kinase concentrations.\textsuperscript{656,657}

Human studies in hypertensive and normotensive subjects of parenteral and oral administrations of L-arginine demonstrate an antihypertensive effect.\textsuperscript{548,658,659,660} The intravenous administration of large doses of L-Arginine acutely reduces BP in normotensive and in salt-sensitive, hypertensive individuals,\textsuperscript{658,659,660} but not in cortisol-induced hypertension in humans. Siani \textit{et al}\textsuperscript{648} evaluated six healthy,\textsuperscript{661} normotensive volunteers in a single-blinded, controlled study utilizing three different isocaloric diets with equal sodium content in each (180 mmol/day) administered in a crossover design in random sequence, each for a one week period. Diet one was the control diet containing 3.5 to 4 grams of L-arginine per day. Diet two contained natural arginine enriched foods at 10 grams of L-arginine per day. Diet three consisted of diet one plus an L-arginine supplement of 10 grams per day. It should be noted that the average arginine intake per day is 5.4 grams/100 grams of protein, which is found especially in lentils, hazelnuts, walnuts and peanuts.\textsuperscript{648} The BP decreased significantly in both diets two and three. In diet two, the BP fall was 6.2/5.0 mm Hg (p < 0.03 for SBP and p < 0.002 for DBP). In diet three, the BP fell 6.2/6.8 mm Hg (p < 0.01 for SBP and p < 0.006 for DBP). In addition, in diet three, creatinine clearance increased (p < 0.07), glomerular filtration rate increased (p < 0.07) and fasting glucose fell (p < 0.008). The reduction in TC and TG with increased HDL in diet two was thought to be secondary to the natural high fiber intake.

L-arginine is not normally the rate limiting step in NO synthesis.\textsuperscript{662} Alternative mechanisms may exist whereby L-arginine lowers BP through direct effects of the amino acid on the vasculature or endothelium, as well as release of hormones, vasodilating prostaglandins, improved renal NO, or endothelial NO bioavailability.\textsuperscript{648}

L-arginine produces a statistically and biologically significant decrease in BP and improved metabolic effect in normotensive and hypertensive humans similar in magnitude to that seen in the DASH-I diet.\textsuperscript{193,648} This reduction in BP was seen whether L-arginine was provided through natural foods or as a pharmacologic supplement when given at approximately a two-fold dietary increase (doses of 10 grams per day).\textsuperscript{648} Although these doses of L-arginine appear to be safe, no long term studies in humans have been published at this time. A good supplemental source of L-arginine is the Heart Bar\textsuperscript{TM} (Cooke Pharmaceuticals, Inc., Silver Springs, Maryland), which supplies 3.3 grams of L-arginine per bar.

HAWTHORN

Hawthorn may reduce SVR and BP,\textsuperscript{14,301,377,663,664} decrease the pressure-rate product in the myocardium, improve ejection fraction and CHF,\textsuperscript{301,663,664} improve arrhythmias,\textsuperscript{663,664} lower cholesterol,\textsuperscript{663} dilate coronary arteries and improve myocardial perfusion and angina.\textsuperscript{301,664} The mechanism of some of these effects is the angiotensin converting enzyme inhibition (ACEI) effect of Hawthorn.\textsuperscript{14,377,665} No controlled clinical trials in hypertensive individuals have been reported to date. Doses of about 160 to 900 mg per day of a standardized extract of Hawthorn have been used to achieve these cardiovascular effects, which appears to be safe.\textsuperscript{663,664} Hawthorn contains oligomeric procyanidins, flavonoids, hyperoside, quercetin, vitexin and vitexin rhamnside, which may also have beta-blocking, calcium-channel-blocking and diuretic effects.\textsuperscript{663} The hypolipidemic effects are due to beta-sitosterol, catechin, chromium, fiber, linoleic acid, magnesium, pectin and rutin, all of which may also reduce BP as well.\textsuperscript{663}
ALCOHOL

Acute and chronic alcohol intake elevates BP and is a risk factor for stroke. Alcohol also causes a biphasic hemodynamic response with initial vasodilation and a subsequent pressor response. Epidemiological observational studies indicate that more than 20 grams of alcohol per day (more than three drinks a day) is associated with both the incidence and severity of hypertension and resistance to antihypertensive therapy. Tsuruta et al reported a 12 year prospective study of 325 normotensive Japanese men with a mean BP < 140/90 mm Hg. The odds ratio was 2.39 to develop hypertension with an alcohol intake of over 46 gm/day versus those consuming less than 46 gm/day, adjusted for age, BMI, SBP, tobacco use and family history. The BP levels were significantly different at p < 0.01 at the conclusion of the study with a BP of 125.2/75 mm Hg in nondrinkers and 134.9/80.2 mm Hg in heavy drinkers. However, this study did not adjust for sodium intake or exercise, and alcohol consumption was self-reported. In the Atherosclerosis Risk in Communities Study (ARIC), consumption of all alcoholic beverages in amounts of ≥ 210 grams per week was an independent risk factor for hypertension.

Numerous observational and clinical studies have consistently demonstrated that reduction or moderation in alcohol intake as well as complete cessation lowers BP and concomitantly increases serum magnesium and potassium. It is recommended that hypertensive patients limit alcohol intake to less than 20 grams per day; that is the equivalent of 10 ounces of wine, 24 ounces of beer or 2 ounces of hard liquor. These amounts do not elevate BP and may be associated with a lower risk of CHD and cancer, and all cause mortality, especially in wine drinkers. The relative risk for death from all causes among wine drinkers was 0.66 (CI 0.55 to 0.77) compared to nondrinkers, and the CHD mortality was significantly lower (p = 0.0007).

CAFFEINE

The hemodynamic and blood pressure effects of caffeine remain controversial and inconclusive. Caffeine elevates BP acutely, but tolerance to this effect develops with chronic ingestion. Most epidemiologic studies do not show a direct relationship between elevated BP and caffeine intake.

Consumption of caffeine at a dose of 3.3 mg per kg will acutely increase SBP 5 to 9 mm Hg and DBP 3 to 8 mm Hg for 30 to 60 minutes in subjects who have avoided caffeine for 12 hours or more. Individuals consuming caffeine 250 mg three times daily for seven days showed significant increase in DBP (p < 0.05) 24 hours after the first intake, but this disappeared in the subsequent days.

Consumption of two to three cups of coffee per day increased BP and cortisol secretion at rest and during stress. The combination of caffeine and stress will elevate BP more than either alone with a mean increase in BP of 12/8 mm Hg. Other studies suggest that the hypertensive and cortisol responses to caffeine occur in habitual users, not just acutely, and there is no tolerance to caffeine's effects. There are obvious individual variations to caffeine's hemodynamic and BP effects. It would be prudent to eliminate or restrict caffeine in most hypertensive patients to less than 100 mg per day.

L-CARNITINE

L-carnitine is a nitrogenous constituent of muscle primarily involved in the oxidation of fatty acids in mammals. Clinical and experimental studies demonstrate significant therapeutic benefits in L-carnitine and its derivative, propionyl-L-carnitine (PLC) in the treatment of diabetes mellitus, hypertension, ischemic heart disease, acute MI, CHF, arrhythmias and peripheral vascular disease with claudication and dyslipidemia. Human studies on the effects of L-carnitine are small and limited. Digiesi et al compared three groups of subjects with essential hypertension. Group A-1, with 14 subjects, received antihypertensive drugs (ACEI and/or CCB) and L-carnitine 2 grams a day. Group A-2, with 14 subjects, received only antihypertensive drugs (ACEI or CCB). Group B, with 9 subjects, was treated with L-carnitine only at 2 grams per day. Group A-1 and B subjects received oral L-carnitine, 2 grams per day for 22 and 10 weeks respectively. Group A-1 subjects had reductions in extrasystoles, improved electrocardiograms (signs of minor changes of ventricular repolarization), less asthenic symptoms (decrease by 90% versus only a 10% decrease in control subjects) and lower TG levels (p < 0.025), but no change in total cholesterol or HDL-C. The group B subjects had improvement in left ventricular ejection fraction from 57.89% to 64.33% (p < 0.001), reduced TC (p < 0.02), and increased HDL-C (p < 0.05) with no change in TG. The BP decreased from a SBP of 155 ± 4.86 mm Hg to 150.89 ± 5.39 mm Hg (NS) and DBP fell from 97.22 ± 1.88 mm Hg to 94.78 ± 2.90 mm Hg (NS).

Carnitine may be useful in the treatment of essential hypertension, type II DM with hypertension, hyperlipidemia, cardiac arrhythmias, CHF and cardiac ischemic syndromes.

Ghidini et al administered L-carnitine, 1 gram, orally twice daily to 38 patients with hypertensive or ischemic heart disease and congestive heart failure in a 45-day placebo-controlled study. Both groups had significant improvement compared to baseline with subjective and objective parameters such as reductions in heart rate (p < 0.01), SBP (p < 0.01), DBP (p < 0.05), edema (p < 0.01), dyspnea (p < 0.01) and significant improvements in exercise tolerance.
0.01), daily digitalis consumption (p < 0.01) and weight (p < 0.01). All patients had a significant diuresis (p < 0.01), improved angina, less arrhythmias, ventricular extrasystoles, echocardiographic changes and moved to a lower NYHA category. However, only the lipid changes and digitalis use were significantly different between groups even though the carnitine-treated patients trended toward more improvement in all parameters. This may have been due to the limited size of the trial population. The TC and TG were significantly reduced only in the carnitine-treated patients (p < 0.05 for TC and p < 0.001 for TG).

TAURINE

Taurine is a sulfonic beta-amino acid that is considered a conditionally-essential amino acid, which is not utilized in protein synthesis, but rather is found free or in simple peptides with its highest concentration in the brain, retina and myocardium. In cardiomyocytes, it represents about 50% of the free amino acids and has a role of an osmoregulator and inotropic factor and has been used to treat hypertension, hypercholesterolemia, arrhythmias, atherosclerosis, CHF and other cardiovascular conditions.

Animal studies have shown consistent and significant reductions in BP. Taurine inhibited the alcohol-induced hypertension in SHR by reducing acetylaldehyde and changing membrane cation handling. In the SHR-high sodium model, taurine reduced proteinuria and lowered BP 20-25%, and reduced LVH, urinary epinephrine, and dopamine. The DOCA-salt rat model had BP reduction due to decreased sympathetic nervous system (SNS) activity centrally due to an opiate-mediated vasodepressor response. Taurine increases renal kallikrein and has an anti-atherosclerotic effect.

Human studies have noted that essential hypertensive subjects have reduced urinary taurine as well as other sulfur amino acids. Taurine lowers BP and HR, decreases arrhythmias, CHF symptoms and SNS activity, increases urinary sodium, and decreases PRA, aldosterone, plasma norepinephrine, and plasma and urinary epinephrine. This diuretic effect is seen in normal subjects as well as hypertensive and cirrhotics with ascites. In doses of 6 grams per day for three weeks in 22 healthy, normotensive, male volunteers, taurine reduced SNS activity, urinary epinephrine, TC and LDL, but increased TG, while BP and BMI did not change significantly. Another study of 31 Japanese males with essential hypertension placed on an exercise program for 10 weeks showed a 26% increase in taurine levels and a 287% increase in cysteine levels. The BP reduction of 14.8/6.6 mm Hg was proportional to both taurine level elevations and plasma norepinephrine reduction. Fujita et al. reduced BP 9/4.1 mm Hg (p < 0.05) in 19 hypertension subjects given 6 grams of taurine for seven days.

The mechanisms by which taurine exerts its cardiovascular and antihypertensive effects include diuresis and urinary sodium loss, vasodilation, increased atrial natriuretic factor (ANF), reduced homocysteine, improved glucose and insulin sensitivity, increased sodium space, reduced SNS activity and opiate mediated vasodepressor response, increased renal kallikrein, reduced PRA and aldosterone, and a glycine mediated CNS response with decreases in both BP and HR.

Concomitant use of enalapril with taurine provides additive reductions in BP, LVH, arrhythmias and platelet aggregation. The recommended dose of taurine is two to three grams per day at which no adverse effects are noted, but higher doses may be needed to reduce BP significantly.

CELERY

Animal studies have demonstrated a significant reduction in BP using a component of celery oil, 3-N-butyl phthalide. There was a dose response relationship in SBP with a 24 mm Hg fall (14%) (p < 0.05) in the Sprague-Dawley hypertensive rat model. Significant decreases in plasma norepinephrine, epinephrine and dopamine were also highly dose dependent. Celery, celery extract and celery oil contain apigenin, which relaxes VSM, CCB-like substances and components that inhibit tyrosine hydroxylase, which reduces plasma catecholamine levels, and lowers SVR and BP. Consuming four stalks of celery per day, eight teaspoons of celery juice three times daily, or its equivalent in extract form of celery seed (1,000 mg twice a day), or oil (one-half to one teaspoon three times daily in tincture form) seems to provide a similar antihypertensive effect in human essential hypertension. In a Chinese study of 16 hypertensive subjects, 14 had significant reductions in BP. Celery also has diuretic effects that may reduce BP. In addition, celery has been used to treat CHF, fluid retention, anxiety, insomnia, gout, and diabetes.

MISCELLANEOUS

1. Nicotinamide Adenine Dinucleotide (NADH)

Nicotinamide adenine dinucleotide (NADH) was shown to significantly reduce SBP in SHR compared to the placebo rats after a 10 weeks oral NADH supplement (p < 0.001). In addition, TC decreased (p < 0.002), LDL decreased (p < 0.02) and measures of renal oxidative stress decreased (p < 0.001). No human studies in essential hypertension with NADH have been done, but therapeutic doses for other medical problems range from 2.5 mg to 20 mg per day orally as the formulation ENADA.
2. Chlorella

A study of 24 hypertensive patients given 10 grams of chlorella tablets and 100 ml of chlorella extract per day had no significant mean change in BP. However, a small subgroup of six patients had a reduction in DBP from 96.5 mm Hg to < 90 mm Hg. Effects on ED, SNS or the replacement of K+, Mg++, Ca++ and fiber may account for the antihypertensive effect.

3. Guava Fruit

Singh et al evaluated 72 patients with essential hypertension treated with 0.5 to 1.0 kg of guava fruit daily for four weeks in a randomized, single-blind, placebo-controlled trial. The patients receiving guava had a net decrease in mean BP of 7.5/8.5 mm Hg (p < 0.05). The high content of soluble fiber and potassium may account for the BP lowering.

4. Herbs

Various herbs and plants have been reported to have antihypertensive effects in animals or humans, but the studies are small and less conclusive or they have only anecdotal-folk uses. These include ashwagandha, jiaogulan, onions and onion oil (botanical relative of garlic), maitake mushrooms, dill, lemon or lemon peel (flavonoids), purslane, yinyanghuo, devil’s claw, kudzu root or tea (isoflavone), guar gum and kaffie potato (flavonoids), reishi, skull cap, siberian ginseng, capsicum (cayenne), fumitoroy (diuretic), ginger (diuretic), angelica, anise, baytree, cashew, echinacea, eucalyptus, german chamomile, ginkgo biloba, indian mulberry, lotus, neem, nutmeg, puncture vine and St. John’s wort.

NUTRITIONAL AND DIETARY SUPPLEMENTS: QUALITY CONTROL AND CERTIFICATION: DIETARY SUPPLEMENT HEALTH AND EDUCATION ACT (DSHEA)

In 1994, the United States Congress passed the Dietary Supplement Health and Education Act (DSHEA), allowing for the marketing of a product claimed to affect the structure or function of the body as a “dietary supplement” without the approval of any government agency, provided the labeling includes a disclaimer saying that it has not been evaluated by the FDA and the product is not intended to diagnose, treat or prevent any disease. A “dietary supplement” in this act is defined as “a vitamin, a mineral, an herb or other botanical or an amino acid”. If a question about safety arises, the burden of proof is on the Food and Drug Administration (FDA), not the manufacturer. No requirement to prove purity exists for dietary supplements sold in pharmacies, health food stores and supermarkets in the United States.

During the past 10 years, however, dietary supplements have been reported to have fewer and less serious side effects than prescription drugs, estimated to be 100,000 deaths per year. Certified, high quality supplements with standardized ingredients that are bioavailable and potent with 100% purity, no toxicity or adverse effects and have accurate labeling and expiration dates should be sought by the wise consumer. The terms “all natural”, “organic”, “herbal”, etc., do not necessarily imply potency, purity, safety, or efficacy.

MEDICATIONS, TOXINS OR DRUGS THAT INCREASE BLOOD PRESSURE

Numerous medications, toxins or drugs have the potential to elevate BP directly or interfere with antihypertensive medications. These include oral contraceptives, nonsteroidal anti-inflammatory drugs (NSAID’s), cyclooxygenase inhibitors (COX-2), decongestant/antihistamine combinations with ephedrine, pseudoephedrine and phenylpropanolamine, corticosteroids, mineralocorticoids, anabolic steroids, ephedra, “energy pills”, “diet pills”, amphetamines, licorice, tricyclic antidepressants, monoamine oxidase inhibitors (MAO), ergot alkaloids, lead, cadmium, thallium, red ginseng, “herbal phen-fen”, cocaine, cyclosporine, erythropoietin, bromocriptine, nasal decongestants, caffeine, tacrolimus, alcohol and others. These should be decreased or eliminated in patients with hypertension.

ANTIHYPERTENSIVE DRUG TREATMENT

Approximately 40 to 50% of patients with essential hypertension may require antihypertensive drug therapy.
Once a diagnosis of essential hypertension is firmly established by JNC-VI guidelines. These drugs should be used in conjunction with the lifestyle modifications, nutritional guidelines, nutraceutical supplements, weight loss, exercise, tobacco cessation, and limited use of alcohol and caffeine as discussed in this paper. Goal BP levels are well established depending on the concomitant medical diseases, risk factors, TOD, and CCD reported in JNC-VI and these should be met to reduce TOD. Selection of drugs and dose will depend on many factors that are best determined by using the Subsets of Hypertension Approach (Table 31).

The primary goal in the treatment of essential hypertension is to prevent and reduce all end-organ damage, not simply to reduce BP. Hypertension is associated with an increased risk of cerebrovascular, cardiovascular and renal morbidity and mortality. Pharmacologic therapy has reduced some, but not all, of these complications. To achieve optimal decreases in morbidity and mortality in hypertensive-related diseases, the overall impact of antihypertensive drug therapy on the pathogenesis of damage to each end organ must be considered.

Although a higher percentage of deaths occurs in patients with diastolic blood pressure (DBP) > 105 mm Hg, patients with DBP ≤ 105 mm Hg actually account for more deaths. The majority of patients (60 to 70%) with essential hypertension have DBP ≤ 105 mm Hg. The risks of therapy versus the benefits of therapy are particularly critical in this group. Pharmacologic therapy of essential hypertension with DBP ≤ 110 mm Hg has reduced the complications of most pressure-related (arteriolar) damage, such as CVA, CHF, and some cases of CRF, but the atherosclerotic complications (CHD, angina, MI, and sudden death) have not been reduced to the extent predicted by the degree of BP reduction in those prospective clinical trials in which diuretics and beta blockers were the primary antihypertensive drugs used. The role of beta blocker monotherapy in reducing CHD in the elderly has been questioned. In addition, beta blockers induce insulin resistance, hyperglycemia, hyperuricemia, and dyslipidemia. The indiscriminate use of diuretics may be associated with a higher incidence of colon and renal cell carcinoma, progressive proteinuria and renal insufficiency, induce hypokalemia, hypomagnesemia, hyperuricemia, hyperglycemia, insulin resistance, homocysteinemia, dyslipidemia, thrombosis and do not seem to optimally reduce CHD.

A more sophisticated and pathophysiologically oriented pharmacologic approach based on our knowledge of vascular biology, endothelial dysfunction, and the complex interplay of the hypertension/atherosclerotic syndrome is needed. The newer drugs such as calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) appear to offer some distinct advantages in both surrogate end points, improvement in vascular remodeling, arterial compliance, endothelial dysfunction and target organ damage, compared to older drugs (diuretics, beta blockers).

The currently FDA-approved single antihypertensive drugs and combination drugs are listed in Table 32 and Table 33. Newer drugs such as CCB, ACEI, and ARB's have distinct advantages on vascular biology (function and structure) as well as many clinical endpoints. These agents also have better metabolic profiles and meet most of the criteria for selection based on the subsets approach to hypertension. They are also coming closer to the characteristics of an ideal antihypertensive drug” (Table 34). In the author’s opinion, CCB, ACEI and ARB’s as monotherapy or in low dose combination are superior to diuretics and beta blockers for the drug treatment of hypertension.

The addition of lifestyle modification with low dose combination antihypertensive drugs (CCB, ACEI, ARB) provides additive or synergistic BP reduction, improved risk factors and metabolic parameters, improved vascular structure and function, allows for lower doses and number of drugs with reduced side effects and may be superior in reducing TOD.

### Table 32

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Daily Adult</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bençaïpar - Lotensin (Novartis)</td>
<td>10-80 mg in 1 or 2 doses</td>
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</tr>
<tr>
<td>Captopril - generic price</td>
<td>12.5-150 mg in 2 or 3 doses</td>
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<tr>
<td>Capoten - Apotex (Canada)</td>
<td></td>
<td></td>
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<tr>
<td>Enalapril - generic price</td>
<td>2.5-40 mg in 1-2 doses</td>
<td></td>
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<tr>
<td>Valsartan (Merck)</td>
<td></td>
<td></td>
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<tr>
<td>Lisinopril - Pipraol (Marck)</td>
<td>10-40 mg in 1 or 2 doses</td>
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</tr>
<tr>
<td>Zestriol (AstraZeneca)</td>
<td>5-40 mg in 1 dose</td>
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</tr>
<tr>
<td>Moexipril - Unverso (Schwarz)</td>
<td>7.5-30 mg in 1 or 2 doses</td>
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</tr>
<tr>
<td>Perindopril - Accord (Sanofi)</td>
<td>4-8 mg in 1 or 2 doses</td>
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</tr>
<tr>
<td>Quinapril - Accupril (Parke-Davis)</td>
<td>5-60 mg in 1 or 2 doses</td>
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<tr>
<td>Ramipril - Altace (Monarch)</td>
<td>1.25-20 mg in 1 or 2 doses</td>
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</tr>
<tr>
<td>Telmisartan - Maxwell (Knod)</td>
<td>1-4 mg in 1 dose</td>
<td></td>
</tr>
</tbody>
</table>

**ANGIOTENSIN II RECEPTOR ANTAGONISTS**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Daily Adult</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan - Coziver (AstraZeneca)</td>
<td>30-60 mg in 1 dose</td>
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<tr>
<td>Esprosart - Treliva (Lundbeck)</td>
<td>400-600 mg in 1 or 2 doses</td>
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<tr>
<td>Irbesartan - Avapro (Bristol-Myers Squibb)</td>
<td>150-300 mg in 1 dose</td>
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<tr>
<td>Losartan - Clozex (Merck)</td>
<td>25-100 mg in 1 or 2 doses</td>
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</tr>
<tr>
<td>Telmisartan - Micardis (Abbott Pharma)</td>
<td>40-80 mg in 1 dose</td>
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</table>
Table 32 Continued

<table>
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<tr>
<th>Drug</th>
<th>Maintenance Dose</th>
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</thead>
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<tr>
<td><strong>ANGOTENSIN II RECEPTOR ANTAGONISTS</strong></td>
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<tr>
<td>Valsartán – Olvan (Novartis)</td>
<td>60-320 mg in 1 dose</td>
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<tr>
<td><strong>BETA-ADRENERGIC BLOCKING DRUGS</strong></td>
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<tr>
<td>Atenolol – average generic price</td>
<td>25-100 mg in 1 or 2 doses</td>
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<td>Nalolol (AstraZeneca)</td>
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<tr>
<td>Betaxolol – average generic price</td>
<td>5-49 mg in 1 dose</td>
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<td>Lopressor (Bristol-Myers Squibb)</td>
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<td>Bisoprolol – average generic price</td>
<td>5-29 mg in 1 dose</td>
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<td>Zebeta (Boehringer)</td>
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<td>Metoprolol – average generic price</td>
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<tr>
<td>Lopressor (Bristol-Myers Squibb)</td>
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<td><strong>Extended release</strong></td>
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<td>Toprol-XL (AstraZeneca)</td>
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<td>Nadolol – average generic price</td>
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<td>Carvedilol – average generic price</td>
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<td>Propranolol – average generic price</td>
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<tr>
<td>Timolol – average generic price</td>
<td>10-40 mg in 2 doses</td>
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<tr>
<td>Blocker (Merck)</td>
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<tr>
<td><strong>Beta-Blockers with intrinsic sympathomimetic activity</strong></td>
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<tr>
<td>Atenolol – average generic price</td>
<td>200-1200 mg in 1 or 2 doses</td>
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<td>Slendale (Wyeth-Ayerst)</td>
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<tr>
<td>Carvedilol – Central (Hoechst)</td>
<td>2.5-10 mg in 1 dose</td>
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<td>Pindolol – Levot (Schwarz)</td>
<td>20 mg in 1 dose</td>
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<td>Pindolol – average generic price</td>
<td>100-50 mg in 2 doses</td>
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<td>Vibental (Boehringer)</td>
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<tr>
<td><strong>Beta-Blockers with Alpha-1 Blocking Activity</strong></td>
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<tr>
<td>Candesart – Coury (GlaxoSmithKline)</td>
<td>12.5-50 mg in 2 doses</td>
</tr>
<tr>
<td>Labetalol – average generic price</td>
<td>200-1200 mg in 2 doses</td>
</tr>
<tr>
<td>Noradepine (Kabi)</td>
<td></td>
</tr>
<tr>
<td>Trandal (GlaxoSmithKline)</td>
<td></td>
</tr>
<tr>
<td><strong>DIURETICS</strong></td>
<td></td>
</tr>
<tr>
<td>Thiazide-Type (usually given daily)</td>
<td></td>
</tr>
<tr>
<td>Chlorothiazide – average generic price</td>
<td>12.5-50 mg</td>
</tr>
<tr>
<td>Dinol (Merck)</td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide – average generic price</td>
<td>12.5-50 mg</td>
</tr>
<tr>
<td>Edeca (Novartis)</td>
<td></td>
</tr>
<tr>
<td>Micardis (Welsh)</td>
<td></td>
</tr>
<tr>
<td>Chlorthalidone – average generic price</td>
<td>12.5-50 mg</td>
</tr>
<tr>
<td>Indapamide – average generic price</td>
<td>1.25-5 mg</td>
</tr>
<tr>
<td>Loop (Aventis)</td>
<td></td>
</tr>
<tr>
<td>Meropenem – Zenapax (Medeva)</td>
<td>1.25-5 mg</td>
</tr>
<tr>
<td>Myaor (Medeva)</td>
<td>0.25 mg</td>
</tr>
</tbody>
</table>

April 2002

Supplement No. 1 JANA 45
### Table 32\textsuperscript{10,749} Continued

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Adult</th>
<th>Maintenance Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALPHA-ADRENERGIC BLOCKERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prazosin – average generic price</td>
<td></td>
<td>First day: 1 mg at bedtime</td>
</tr>
<tr>
<td>Minipress (Pfizer)</td>
<td></td>
<td>Maintenance: 1-20 mg in 2 or 3 doses</td>
</tr>
<tr>
<td>Terazosin – average generic price</td>
<td></td>
<td>First day: 1 mg at bedtime</td>
</tr>
<tr>
<td>Hytrin (Abbott)</td>
<td></td>
<td>Maintenance: 1-20 mg in 1 dose</td>
</tr>
<tr>
<td>Doxazosin – average generic price</td>
<td></td>
<td>First day: 1 mg at bedtime</td>
</tr>
<tr>
<td>Cardura (Pfizer)</td>
<td></td>
<td>Maintenance: 1-16 mg in 1 dose</td>
</tr>
<tr>
<td><strong>CENTRAL ALPHA-ADRENERGIC AGONISTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine – average generic price</td>
<td>0.1-0.6 mg in 2 or 3 doses</td>
<td></td>
</tr>
<tr>
<td>Catapres (Boehringer Ingelheim)</td>
<td></td>
<td>one patch weekly (0.1 to 0.3 mg/day)</td>
</tr>
<tr>
<td>transdermal – Catapres TTS (Boehringer Ingelheim)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guanabenz – average generic price</td>
<td>4-64 mg in 2 doses</td>
<td></td>
</tr>
<tr>
<td>Wydase (Wyeth-Ayerst)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guanfacine – average generic price</td>
<td>1-3 mg in 1 dose</td>
<td></td>
</tr>
<tr>
<td>Tenex (Robins)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylphenidate – average generic price</td>
<td>250 mg-2 grams in 2 doses</td>
<td></td>
</tr>
<tr>
<td>Altarex (Morok)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DIRECT VASODILATORS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydralazine – average generic price</td>
<td>4-200 mg in 24 doses</td>
<td></td>
</tr>
<tr>
<td>Minoxidil – average generic price</td>
<td>2.5-40 mg in 1 or 2 doses</td>
<td></td>
</tr>
<tr>
<td>London (Pharmacia &amp; Upjohn)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PERIPHERAL ADRENERGIC NEURON ANTAGONISTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guanethidine – Hydrochloride (Mestona)</td>
<td>10-75 mg in 2 doses</td>
<td></td>
</tr>
<tr>
<td>Reserpine – average generic price</td>
<td>0.05-0.1 mg in 1 dose</td>
<td></td>
</tr>
</tbody>
</table>

### Table 33\textsuperscript{10} Continued

<table>
<thead>
<tr>
<th><strong>SELECTED COMBINATION ANTIHYPERTENSIVE DRUGS</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-Adrenergic Blockers and Diuretics</td>
<td></td>
</tr>
<tr>
<td>Atenolol, 50 or 100 mg/chlorthalidone, 25 mg</td>
<td>Tenoretic</td>
</tr>
<tr>
<td>Bisoprolol fumarate, 2.5, 5, or 10 mg/chlorthalidone, 6.25 mg</td>
<td>Ziac</td>
</tr>
<tr>
<td>Metoprolol tartrate, 50 or 100 mg/chlorthalidone, 20 or 50 mg</td>
<td>Lopressor HCT</td>
</tr>
<tr>
<td>Nadolol, 40 or 80 mg/chlorthalidone, 5 mg</td>
<td>Catzido</td>
</tr>
<tr>
<td>Propranolol hydrochloride, 40 or 80 mg</td>
<td>Intercide</td>
</tr>
<tr>
<td>hydrochlorothiazide, 25 mg</td>
<td></td>
</tr>
<tr>
<td>Propranolol hydrochloride (extended release), 80, 120, or 160 mg/hydrochlorothiazide, 50 mg</td>
<td>Intercide LA</td>
</tr>
<tr>
<td>Timolol maleate, 10 mg/hydrochlorothiazide, 25 mg</td>
<td>Timolide</td>
</tr>
</tbody>
</table>

### Table 34\textsuperscript{10}

**CHARACTERISTICS OF THE IDEAL ANTIHYPERTENSIVE DRUG**

1. Efficacious as a monotherapy in more than 50% of all patients.
2. BP control during all activities for 24 hours.
3. Once-a-day dosing with high trough to peak ratio.
4. Hemodynamically logical and efficacious: reduces SYR, improves arterial compliance, preserves CO and maintains perfusion to all vital organs.
5. Lack of tolerance or pseudotolerance: no reflex volume retention or stimulation of neurohumoral mechanisms.
As has been discussed previously, many of the natural compounds in food, certain nutraceutical supplements, vitamins, antioxidants, or minerals function in a similar fashion to a specific class of antihypertensive drugs. Although the potency of these natural compounds may be less than the antihypertensive drug, when used in combination with other nutrients and nutraceuticals, the antihypertensive effect is magnified. In addition, many of these nutrients and nutraceuticals have varied, additive, or synergistic mechanisms of action in lowering BP. Table 35 summarizes these natural compounds into the major antihypertensive drug classes such as diuretics, beta blockers, central alpha agonists, CCB, ACEI and ARB’s.

**SUMMARY AND CONCLUSIONS**

1. Vascular biology (ED and VSM dysfunction) plays a primary role in the initiation and perpetuation of hypertension, CVD, and TOD.
2. Nutrient-gene interactions are a predominant factor in promoting beneficial or detrimental effects in cardiovascular health and hypertension.

3. Nutrition (natural whole food, nutraceuticals) can prevent, control and treat hypertension through numerous vascular biology mechanisms.


5. Antioxidants can prevent and treat hypertension.

6. Whole food and whole food concentrates of fruits, vegetables and fiber with natural combinations of balanced phytonutrients, phytochemicals, antioxidants, vitamins, minerals and appropriate macronutrients and micronutrients are generally superior to single component or isolated artificial or single component natural substances for the prevention and treatment of hypertension and CVD.

- However, there is a role for the selected use of single and component nutraceuticals, vitamins, antioxidants and minerals in the treatment of hypertension based on scientifically controlled studies as a complement to optimal nutritional, dietary intake from food and other lifestyle modifications.

- Exercise, weight reduction, smoking cessation, and alcohol and caffeine restriction, as well as other changes in lifestyle must be incorporated.

7. Specific mechanism of actions of nutrition and nutraceuticals include:

- **ACEI activity:** garlic, seaweed, tuna, sardine, dry salted fish, zein, fish sauce, chicken, egg yolks, hydrolyzed whey protein, hawthorne, sour milk, gelatin, sake, bonito, pycnogenol, casein, omega-3 fatty acids, zinc, wheat germ hydrolysate.

- **CCB activity:** ALA, vitamin C, vitamin B₆, Mg++, NAC, vitamin E, hawthorne, celery, omega-3 fatty acids, Ca++, garlic.

- **ARB activity:** K⁺, fiber, garlic, vitamin C, vitamin B₆, coenzyme Q-10, celery, GLA and DGLA.

- **Diuretic:** hawthorne, vitamin B₆, taurine, celery, GLA, vitamin C, K⁺, Mg++, Ca++, protein, fiber.

- **Beta blockers:** hawthorn

- **NO increased:** L-arginine, omega-3 PUFA, garlic, vitamin C, vitamin E, ALA, NAC, Mg++, K⁺, MUFA, CoQ₁₀.

- **Reduced activity or sensitivity to angiotensin-II and NE:** K⁺, fiber, garlic, vitamin C, vitamin B₆, CoQ₁₀, taurine, celery, GLA and DGLA, zinc, protein, Na⁺ restriction.

- **Gene expression NFkB:** Zn, vitamin E, ALA.

- **AGE and RAGE:** omega-3 PUFA, fiber.

- **PPAR alpha ligand:** omega-3 PUFA.

- **SREBP-1:** omega-3 PUFA.

- **Antioxidants:** neutralize ROS, O₂⁻: numerous other effects.

- **Insulin sensitivity:** fiber, omega-3 PUFA, vitamin C, vitamin E, vitamin D, vitamin B₆, CoQ₁₀, ALA, taurine, K⁺, Mg++, Zn, L-arginine, L-carnitine.

- **Increased PGI₂, PGE₁, PGE₃:** vitamin C, niacin, Zn, omega-3 fatty acids, vitamin E, selenium, Ca++, Mg++, GLA and DGLA (omega-6 FA), L-arginine

- **PKC inhibition:** vitamin E.

- **Increased cytosolic Mg++:** vitamin E.

- **TK inhibition:** SO₄, flavonoids, genistein, diadzein.

- **↓PRA, ↓aldo:** Taurine, GLA, DGLA, vitamin B₆, CoQ₁₀.

- **↑ANF:** Taurine.

- **Improved arterial compliance:** Na⁺ restriction, K⁺, Mg++, soy, garlic, vitamin E, ALA.

- **Reduced VSM hypertrophy:** Na⁺ restriction, K⁺, vitamin E, COQ₁₀, ALA.

- **Microalbuminuria reduction:** Na⁺ restriction.

- **Modulates baroreceptor sensitivity:** K⁺.

- **Direct vasodilation:** K⁺, Mg++, Ca++, fiber, garlic, vitamin C, flavonoids, CoQ₁₀, ALA, L-arginine, taurine, celery, MUFA, soy, omega-3 FA, vitamin E.

**RECOMMENDATIONS**

<table>
<thead>
<tr>
<th>Nutrition</th>
<th>Daily Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. DASH I and DASH II-Na⁺ diets</td>
<td></td>
</tr>
<tr>
<td>2. Sodium restriction</td>
<td>50 – 100 mmol</td>
</tr>
<tr>
<td>3. Potassium</td>
<td>60 – 100 mEq</td>
</tr>
<tr>
<td>4. Potassium/sodium ration</td>
<td>&gt; 5:1</td>
</tr>
<tr>
<td>5. Magnesium</td>
<td>500 – 1000 mg</td>
</tr>
<tr>
<td>6. Calcium</td>
<td>1000 – 1500 mg</td>
</tr>
<tr>
<td>7. Zinc</td>
<td>25 mg</td>
</tr>
<tr>
<td>8. Protein: total intake (40% total calories)</td>
<td>1.0 – 1.5 mg/kg</td>
</tr>
<tr>
<td>A. Nonanimal sources preferred but lean or wild animal protein in moderation is acceptable</td>
<td></td>
</tr>
<tr>
<td>B. Hydrolyzed whey protein</td>
<td>5 grams</td>
</tr>
<tr>
<td>C. Soy protein (fermented is best)</td>
<td>30 grams</td>
</tr>
<tr>
<td>D. Hydrolyzed wheat germ isolate</td>
<td>2 – 4 grams</td>
</tr>
<tr>
<td>E. Sardine muscle concentrate extract</td>
<td>3 mg</td>
</tr>
<tr>
<td>F. Cold water fish, fowl poultry</td>
<td></td>
</tr>
<tr>
<td>9. Fats: 25% total calories</td>
<td></td>
</tr>
<tr>
<td>A. Omega-3 fatty acids (30%) PUFA</td>
<td>3 – 4 grams</td>
</tr>
<tr>
<td>B. Omega-6 fatty acids (10%) PUFA</td>
<td>(DHA, EPA, ALA, cold water fish)</td>
</tr>
</tbody>
</table>
C. Omega-9 fatty acids (30%) MUFA ....4 tablespoons (extra virgin olive oil)
D. Saturated FA (lean, wild animal meat) (30%)
E. P/S ratio (polyunsaturated/saturated) fats > 2.0
F. No trans-fatty acids (0%) (hydrogenated margarines, vegetable oils)
H. Nuts: almonds, walnuts, hazelnuts, etc.

10. Carbohydrates (35% total calories)
A. Reduce or eliminate refined sugars and simple carbohydrates
B. Increase complex carbohydrates and fiber whole grains (oat, barley, wheat)
   \( i.e. \) oatmeal ...................60 grams
   \( \text{oatbran (dry)} \) ...........40 grams
   beta-glucan ......................3 grams
   psyllium ..........................7 grams

11. Garlic ..................................................4 cloves/4 grams

12. Mushrooms (shiitake and maitake)

13. Guava fruit..........................................500 – 1000 mg

14. Wakame seaweed (dried)....................3.0 – 3.5 grams

15. Celery
celery stalks ..................................4 stalks
celery juice ..................................8 teaspoons TID
celery seed extract ......................1000 mg BID
celery oil (tincture) ..............1/2 – 1 teaspoon TID

16. Lycopene ............................................10 mg
   Tomatoes and tomato products, guava, watermelon, apricots, pink grapefruit, papaya

**Nutrition**

<table>
<thead>
<tr>
<th>Exercise</th>
<th>Daily Intake</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobic</td>
<td>7 days/weeks</td>
<td></td>
</tr>
<tr>
<td>45 minutes daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4200 Kcal/week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resistance training daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>To ideal body weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lose 1 – 2 pounds/week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMF ( \leq 25 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist circumference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 35 inches in female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 40 inches in male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total body fat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 16% in males</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 22% in females</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Increase lean muscle mass

Alcohol Restriction ...................................< 20 grams/day
Wine < 10 ounces
Beer < 24 ounces
Liquor < 2 ounces (100 proof whiskey)

Caffeine Restriction ..................................< 100 mg/day

**Tobacco and Smoking** ............................STOP
Avoid drugs and interactions that increase BP (see list)

**VITAMINS, ANTIOXIDANTS AND NUTRACEUTICAL SUPPLEMENTS**

**Daily Intake**

- Vitamin C ...........................................250 to 500 mg BID
- Vitamin E .........................................400 to 800 IU QD
- Vitamin B-6 ......................................100 mg QD to BID
- Co-enzyme Q-10 (QGEL®) .....................60 mg QD to BID
- Lipoic Acid .....................................100 to 200 mg BID
- N-Acetyl Cysteine ..............................500 mg BID
- L-Arginine (Heart Bar®) (3.3 grams) ....one bar BID
  (plus lentils, hazelnuts, walnuts, peanuts)
- Hawthorne Standardized Extract ..........160 – 900 mg QD
- L-Carnitine .....................................1000 mg BID
- Taurine ..........................................1.0 to 1.5 grams BID
- ΣNADA .............................................2.5 to 5.0 mg BID

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