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

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Vascular Disease is a Balance

Vascular Injury
vs
Vascular Repair

“The blood vessel has a finite number of responses to an infinite number of insults.”

Mark Houston MD,MS 2002

Hypertension is not a disease, it is the “correct” but chronic dysregulated response with an exaggerated outcome of the infinite insults to the blood vessel with the subsequent environmental-gene expression patterns in which the vascular system is the innocent bystander.

This Environment-Gene Interaction is a combination of the infinite biomechanical and biohumoral (biochemical, metabolic and nutritional insults)

Modulation of the environmental insults as well as the downstream disturbances of gene expression patterns is the key to the prevention and treatment of hypertension and cardiovascular disease. Role of vascular “Neo-antigens” secondary to damaged proteins

Houston 2011
Hypertension, Vascular Biology and the Blood Vessel

Eftekhari A et al. J of Hypertension 2011; 29: 896--905

- Hypertension is not a disease but is a marker for vascular dysfunction.
- An elevated blood pressure is one of many responses of the blood vessel to endothelial dysfunction, vascular smooth muscle dysfunction and impaired microvascular function and structure.
- Endothelial dysfunction and microvascular smooth muscle dysfunction precede the development of hypertension by decades.

Vascular Endothelium: Strategic Anatomical Position

Houston MC. Vascular Biology in Clinical Practice. Hanley and Belfus, Philadelphia 2000

The Endothelium Maintains Vascular Health

Houston MC. Vascular Biology in Clinical Practice. Hanley and Belfus, Philadelphia 2000

Balance of Nitric Oxide vs Angiotensin II


- ANGIOTENSIN II IS VASOCONSTRICTIVE HYPERTENSIVE, INFLAMMATORY, INCREASES OXIDATIVE STRESS, VASCULAR IMMUNE DYSFUNCTION, THROMBOSIS, GROWTH AND IS PROATHEROGENIC.
- NITRIC OXIDE IS VASODILATORY, ANTI-HYPERTENSIVE, ANTI-INFLAMMATORY, REDUCES OXIDATIVE STRESS, REDUCES VASCULAR IMMUNE DYSFUNCTION AND THROMBOSIS AND IS ANTIATHEROGENIC.
Endothelial Dysfunction (ED)

**Characterized by** decreased release of relaxing factors (vasodilators) and propensity to secrete contracting factors (vasoconstrictors).

**Key, initial and earliest event in vascular disease. Present with only risk factors but no atherosclerosis.**

**Precedes intimal thickening and clinical atherosclerosis by a decades.**

**Correlation with future CV events (MI, PCTA, CABG, sudden death).**

**Diverse pathophysiologic stimuli are capable of inducing similar nonadaptive changes in endothelial function."**

**Syndrome of Endothelial Dysfunction (ED).**

**Hypertension (1 and 2) has reduced EDV in both peripheral and coronary arteries.**

**Two Paradigms of Endothelial Activation:**

**Biochemical and Biomechanical**

**Endothelial Dysfunction**

**Pathophysiologic Stimuli and Consequences**

Dysregulated Flow

Inflammatory cytokines

Oxidant products

Advanced Glycosylation End Products

Hypertension

Endothelial Dysfunction

Increased Sympathetic tone

Increased Endothelin

Impaired Nitric Oxide bioavailability

Reduced EDRF

Increased Proliferation & Migration

Increased Prothrombotic activity

Impaired Vasorelaxation

Retinal neovascularization

Inflammation

Endothelial activation

Autocrine & Paracrine

Increased permeability & transport

Increased leukocyte adhesion & chemotaxis

Increased procoagulant activity

Disproportionally impaired microvascular structure in essential hypertension.

Effekhari A et al. J of Hypertension 2011; 29:896-905

- The level of BP elevation does not give an accurate indication of the microvascular involvement and impairment in hypertension.

- Hypertensive patients have abnormal microvascular in the form of inward eutrophic remodeling of the small resistance arteries leading to impaired vasodilatory capacity, increased vascular resistance, increased media to lumen ratio, decreased maximal organ perfusion and reduced flow reserve. In the heart, this is CFR (coronary flow reserve).
Microvascular impairment precedes the development of hypertension

- Significant structural microvascular impairment occurs long before the BP begins to rise in normotensive offspring of hypertensive parents.
- Diastolic dysfunction, increased LVMI and LVH may also occur early in these offspring but is a later development that is related more to cardiac and vascular structural dysfunction, large artery impairment and loss of arterial compliance and elasticity.

Hypertension is a disease of the blood vessel.

- Which occurs first: The hypertension or the diseased blood vessel, or is it both? It is bidirectional.
- Hypertension is part of vascular disease and vascular aging. A marker of vascular dysfunction.
- The best approach to manage hypertension is to improve vascular health, optimize vascular biological function and structure and slow vascular aging and subsequent CVD.

PATHOPHYSIOLOGY OF HYPERTENSION
J of the American Society of Hypertension 2010;4:272
Circulation 2007;115:1020
Expert Rev in CV Therapy 2010;8:821
Nephrol Dial Transplant 2006:21:850

1. Oxidative Stress (ROS and RNS) is increased in the arteries and kidneys with a concomitant decreased oxidative defense.
2. Inflammation is increased in the vasculature and kidneys: increased HSCRP, increased neutrophils and decreased lymphocytes. Increased RAAS activity in the kidney.
3. Autoimmune dysfunction of the arteries and kidneys: increased WBC, and involvement of CD4+( T-helper cells) and CD 8+(cytotoxic T –cells)
4. Abnormal vascular biology with Endothelial dysfunction (ED) Vascular smooth muscle (VSM) dysfunction
5. Genetics, Epigenetics and Environmental-genomic interaction

Inflammation: High Sensitivity C- Reactive Protein (HSCRP) downregulates Vascular AT2R Receptor
Circulation 2007;115:1020
Am Heart J 2009;158:277

- Increased inflammation and HSCRP levels increase BP
- HSCRP is both a risk marker and risk factor for hypertension: bidirectional
- Predicts CVD and all cause mortality
- HSCRP increases BP in just a few days
- Small increases of HSCRP over 3 ug/ml increase BP. The higher the HSCRP the higher the BP
- HSCRP inhibits eNOS and reduces nitric oxide (NO)
- NO regulates AT2R
- HSCRP downregulates AT2R. This increases BP and CVD risk. AT2R when stimulated lowers BP and CVD. AT2R counterbalances the AT1R which increases BP and CVD. AT1R is inflammatory, increases oxidative stress and vascular immune dysfunction

Inflammation Increases BP: HSCRP, Leukocytosis and Autoimmune dysfunction
J of Am Society of Hypertension 2010;4:272

- HSCRP increases BP and hypertension increases HS CRP. Bidirectional risk.
- HSCRP is the best vascular inflammation marker. Composite of vascular and nonvascular sources of TNF alpha, IL 6 and IL 1b via hepatic production.
- Leukocytosis, especially increased neutrophils and decreased lymphocyte count, increase BP especially in Blacks. The SBP is 6 mm Hg higher and DBP 2 mmHg higher from highest to lowest quartiles.
- Dysregulation of CD4+ and CD8+ T lymphocytes in hypertension and CVD.
Caveolae: A regulatory platform for nutritional modulation of vascular inflammation

J of Nutritional Biochemistry 2011;22:807

- Caveolae are lipid raft microdomains abundant within the lipid bilayer of the plasma membrane of endothelial cells.
- Responsible for modulating receptor-mediated signal transduction and thus influencing endothelial activation, macrophage/monocyte recruitment, subendothelial lipid accumulation and thus atherosclerotic vascular disease and hypertension.
- Influence and regulate enzymes associated with several key enzymes capable of determining intracellular redox status, increasing ROS and decreasing NO bioavailability.
- Diet and plasma derived nutrients modulate an inflammatory outcome by interacting with and altering caveolae formation of ROS and increasing NO bioavailability.

- Caveolin-1, a protein in caveolae, facilitates and is necessary for the development of vascular disease and atherosclerosis.
- Caveolin-1 deficiency retards atherosclerosis in mice.
- Caveolin-1 deficiency down-regulates CAMS like VCAM and CD-36 SR.
- Caveolin-1 decreases NO in response to IL-6, IL-1b, TNF alpha. LPS stimulates Nrf2, decreases BH4 and is cofactor for NADPH-oxidase action.
- Reduces antioxidant defense via Nrf2.
- Decreases mitochondrial biogenesis and redox status via AMPK.
- oxLDL translocates Caveolin and eNOS from lipid rafts.

Caveolae: Therapeutic Interventions

J of Nutritional Biochemistry 2011;22:807

Omega 3 fatty acids especially DHA

- Alter lipid environment of raft microdomains and downstream signaling events.
- Lipid raft disruption.
- Decreased lipid raft cholesterol with reduced ICAM and VCAM response to TNF alpha.
- Displace Caveolin-1, increase eNOS and increase NO.
- Modulate TLR 4 activation response to LPS and lauric acid.
- Inhibits NADPH oxidase induced superoxide production.
- Attenuates atherosclerosis and hypertension.

- Plant-derived polyphenols
  - Fruits and vegetables
  - Resveratrol
  - Quercetin
  - Red wine
  - Tea: EGCG
  - Dark Chocolate
  - Various Flavonoids
  - Diadzein and genistein

Decrease inflammatory stimulation for endothelial activation.
Selectively and avid uptake into caveolae.
Increase NO.
Increase mitochondrial uptake of compounds.

Atherosclerosis, Hypertension and Vascular Disease Related to Meals

J of Nutritional Biochemistry 2011;22:807
Exp Mol Med 2010;42:245

- Atherosclerosis and vascular disease is a post-prandial phenomena.
- Inflammatory foods induce oxidative stress, autoimmune vascular dysfunction, endotoxemia with bacterial product absorption and inflammation.
- Hypertension is primarily a vascular disease with the above components.

- Monocytes, macrophages and CD4+ T lymphocytes invade the arterial wall with TLR like receptor(TLR) involvement.
- CD4+ cells attracted by chemotactic proteins, RANTES (Regulated upon activation normal T-cell expressed and secreted) and SDF-1 (stromal cell derived factor -1).
- CD4+ cells enter as T-helper 0 cells, encounter antigens and convert into T-helper cells.
- Release pro-inflammatory mediators, TNF alpha, interferon, interleukins.
- CD4+ cells express AT1R and PPAR gamma receptors.
- AT-II activates T cells, macrophages and dendritic cells.
- Inflammatory response involving T cells may be triggered by oxidative stress in the nuclei of the brain and increase BP.
Autoimmune dysfunction and Hypertension and CVD
Curr Opin Nephrol Hypertens 2011;20:113
- IL-17 produced by T cells plays a pivotal role in the genesis of hypertension caused by Angiotensin II.
- In IL-17 deficient mice a chronic A-II infusion did not result in chronic sustained hypertension.
- HIV positive men with reduced CD4+ T cells are less prone to systolic hypertension than HIV negative men.
- T-reg cells reduce cardiac damage in mice given A-II infusions and hypertension.

Aldosterone is a modulator of immunity, hypertension and CVD
J of Hypertension 2011;29:1684
- Aldosterone is an independent risk factor for CVD.
- Mineralocorticoid receptors exist in heart, blood vessels, brain and immune cells.
- Blockade of aldosterone even with persistence of hypertension and in normotensive patients reduces CV risk.
- Aldosterone mediated non-hemodynamic effects increase CVD.
- Aldosterone is associated with increased adaptive immunity and autoimmune responses with CD4+ T cell activation and Th 17 polarization, increased IL-10, TGF-B and TNF alpha which modulate over 30 inflammatory genes.

Autoimmune dysfunction and hypertension and CVD : Summary
- Activation of the immune system plays a casual role in the pathogenesis of hypertension and hypertension-induced target organ damage and CVD.
- The antigens involved in the immune activation are infinite
- APC’s activate T cells which enter the target organs and promote damage
- Different macrophage subtypes can either amplify the inflammatory response, help in the repair process or counter-regulate the disease process.
- Both A-II and aldosterone increase immune responses and increase IL-17 levels.

Polymorphisms of anti-oxidant enzymes, blood pressure and risk of hypertension
Journal of Hypertension 2011;29:492
- Chronic oxidative stress increases the risk for hypertension
- Increase in pro-oxidant enzymes like NADPH oxidase and xanthine-oxidase
- Reduction in cytoplasmic anti-oxidant systems
- Polymorphisms for CYBA for NADPH oxidase
  Xanthine-oxidase gene
  SOD 3 : c.172G>A
  Catalase: c.-20C>T
  GPx1: c.*891C>T
  TXN (thioredoxin): c.-793T >C ( NFKb, AP-1, Ref-1, SP -1) and DNA binding to transcription factors.

Genetics of Hypertension Polygenetics
Korkor et al: International J. of Medical Sciences 2011 pending publication
J of the American Society of Hypertension 2009;3:231
- Micro-array analysis of differential gene expression in peripheral blood cell found 31 up-regulated and 18 down regulated genes
- MHC class II receptor activity and immune response.
- Increase HS CRP in hypertensive patients
- Increased inflammation genes

Conclusion: Hypertension is an inflammatory and autoimmune disease

HYPERTENSION
- Normal BP is 120/80 mmHg but risk for CVD starts at 110/70.
- Both SBP and DBP are a continuum of risk starting at 110/70 mm Hg. Increase 20/10 mm Hg doubles risk.
- Before age 50-55 the DBP predicts risk best.
- After age 50-55 the SBP predicts risk best.
- Pulse pressure may be better predictor than SBP or DBP
- Proper technique per AHA guidelines.
- 24 hour ABM more accurate than office BP and better predictor of CV events.
- Central arterial pressure is better then office or ABM.
- Mercury cuffs best. Electronic arm cuffs not wrist or finger cuffs. Proper instruction for patients.
- Mean BP and variability are important to measure
- BP load : % readings > 140/90 should be less than 15 %
**HYPERTENSION: Blood Pressure: New Concepts**

- **Dippers (10-20 % difference) vs non dippers (0-10%) difference in night and day BP**  
  Excessive dipping increases ischemic CVA and reverse dipping increases ICH. Non dippers have increased platelet volume
- **Reverse dipping (0 %) and extreme dipping > (20%)**  
  Baro-receptor dysfunction and sensitivity
- **AM BP surges increase CVA risk, MI risk and LVH**
- **Role of oxidative stress, A II, NE, MMPs and ICH**
- **Central BP better than brachial BP measurements (Expert Rev Cardiovasc Ther. 2010;8:260)**
- **Pulse wave contour, augmentation index and PWV : three types with same SBP but with different risk**
- **BP variability increases CV risk**
- **White coat hypertension increases CV risk**
- **Masked hypertension (also with higher glucose and MAU) 10 % incidence, M>F (J Clin Hypertension 2010;12:578.)**
- **Nondipping does not allow for renal sodium excretion**
- **Nondipping is highly correlated with CHD, CVD, CVA, LVH, CHF, CRF, increased carotid IMT, multifocal leukoencephalopathy (MFLE) and silent cerebral infarctions (SCI).**
- **Nondipping most common in Sodium sensitive patients and Blacks**
- **Renal insufficiency**
- **Secondary forms of hypertension**
- **Diabetes mellitus**
- **Loss of cerebral volume / cognitive impairment**
- **LVH**
- **Refractory hypertension**
- **OSA**

**Hypertension: Blood Pressure New Concepts :Sleep BP**

- **Awake BP controlled by SNS**
- **Asleep BP controlled by RAAS and SNS**
- **Lower BP at sleep is more powerful predictor of outcome that awake BP**
- **Lack of BP dipping related to renal sodium reabsorption. These respond to diuretics**
- **Drugs with dual action on SNS and RAAS control awake and sleep BP**
- **RAAS drugs work best at night.**
- **Normal sleep BP is 108/63 and wake BP is 135/78 mm Hg in normotensives (27/15 mm)**
- **Most drugs may partially convert non-dippers to dippers if given at night.**

**HYPERTENSION: New Definition of Hypertension**

- **J of Hypertension 2006;8:5-14**
- "Hypertension is a progressive cardiovascular syndrome arising from complex and inter-related etiologies, which features early markers that are often present before blood pressure elevation is sustained."

- **ASH definition**

**Central Blood Pressure**

- **Expert Rev Cardiovasc Ther 2010;8:763**
- **Circulation 2006;113:1213 (CAFÉ Trial)**
- **J of Hypertension 2010;28:237**
- **Journal of Hypertension 2011;29:454**
- **CBP is the ascending aortic BP**
- **More predictive of CVD, CVD mortality, all cause mortality and LVH than brachial BP**
- **CBP indicates pressure exerted on heart and brain**
- **CAFÉ study indicated that CVD outcome related to CBP better than brachial pressure and CVD. The CBP is different depending on the anti-hypertension drug class. BB and diuretics lower brachial BP but SBP is 4.3 mm Hg higher and central aortic pulse pressure was 3.0 mm Hg higher. Due to pulse wave augmentation. Range in studies is 3.3 to 4.3 mm Hg.**
- **CBP reduced by CCB, ACEI, ARB and alpha blockers**
- **CBP is increased or unchanged by BB and diuretic**

**Blood Pressure Regulation during the aging process: The end of the "hypertension era"?**

- **Standard BP measurements are not adequate and often misleading and may not accurately reflect CV risk**
- **Need direct arterial measurements**
- **ENDOPAT or DTM to measure endothelial dysfunction**
- **PWV and CAPWA to assess small artery compliance, small vessel vascular remodeling and large arterial stiffness. PWV less than 12 m/s is normal**
- **Central and peripheral arterial waveforms including pulse wave analysis and wave reflections**
- **Central Arterial Pressure, pulse pressure and central to peripheral pressure amplification.**
- **24 hour ABM**
- **Home BP**
Pre-hypertension subtype with an elevated HS CRP increases the risk of stroke

Hypothesis
- Hypertension
- Environment
- Genetics
- Macro & Micronutrients
  - Crucial in regulation of BP
  - Subsequent target organ damage
- Nutrient-Gene interactions & expression (Nutragenomics)
  - Positive or negative effect on vascular biology

The Hypertension Syndrome – It’s More Than Just Blood Pressure

Key Concept in Endothelial Dysfunction, Atherosclerosis, Cardiovascular Disease, and CHD

New Treatment Approach

Weight Loss and BP
Masuo K. et al. Hypertens Res 2011;Aug 4 EPUB
Bischoff SC et al. Int J Obes (Lond);2011;June 14 EPUB

- One of the most effective means to reduce BP - observational and clinical trials show positive direct relationship
- 4-5 Kg weight loss significantly lowers BP (7 / 5 mmHg) in obese and non-obese individuals. Visceral obesity most important. Body fat reduction more important than weight reduction. Maintain lean muscle mass. Men< 16 % and women < 22% body fat with normal WC and WHR.
- Additive to other nonpharmacologic and pharmacologic treatment
- More effective in BP reduction when combined with exercise
- Reduces BP before and without achieving IBW
- Reduces frequency of hypertension by about 18%
- Reduces adipokines which increase BP and inflammation

ACEI Inhibitors
- ACEI
- ARB’s
- CCB’s

AT blockers
- IRA
- VPI’s
- ET1B’s

Calcium channel blockers
- BB
- D

Central Alpha Agonists
- CAR

Alpha Blockers
- AB
Weight Loss and BP

- Role of hyperinsulinemia, insulin resistance, ↑ IVF, ↑ SNS activity, ↑ SVR, Na+ retention, PRA, Aldosterone, sleep apnea adipokines, inflammation (HSCRPs).
- Direct dose-response relationship
- Meta-analysis: 11 Clinical Trials
  - SBP: 1.6 mmHg / Kg weight loss
  - DBP: 1.1 mmHg / Kg weight loss
- Short term and long term effects persist, but only 13% maintain weight loss at 36 months

Exercise and Hypertension

- Meta-analysis of 13 controlled trials: mean BP reduction 11.3/7.5 mm Hg
- NEJM 1981; 304: 930-3
- Prog Cardiovas Disease 1999; 41: 651-60
- Current Atherosclerosis Report 2000; 2: 521-8
- J Hypertens 1998; 7: S19-S23
- JAMA 1993; 270: 713-24
- JAMA 1993; 279: 839-46
- Circulation 1986; 73: 30-9

Exercise and Hypertension

- Role of eNOS and NO: Endothelial function, ED, CABF, SVR, insulin resistance, anabolic hormones, interleukin 10 and other muscles hormones.
- Requires 5-7 days/week with interval training for 20 min daily and resistance training 40 minutes daily to reduce BP and lower CVD
- 4200 KJ/ week required to reduce CHD
- Increases lean body mass, decreases % body fat
- BP reduction occurs in dose response pattern

Nutrient Regulation of Gene Expression: Nutragenomics

- Nutrient
  - “Interaction Action” Not Parallel Action
  - Beneficial Outcome
  - Detrimental Outcome
  - Lower Lipids
  - Lower Glucose
  - Lower BP
  - Lower Cancer Risk
  - Reduce Cardiovascular Risk

Summary of BP Reductions in DASH-I and DASH-II Na+ Diets Hypertensive Patients and Overall

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<tr>
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<th>SBP</th>
<th>DBP</th>
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<tr>
<td>DASH-I Overall Comb.</td>
<td>-5 mmHg</td>
<td>-3 mmHg</td>
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<tr>
<td>DASH I Hypertensive Pts. Comb.</td>
<td>-10.7 mmHg</td>
<td>-5.2 mmHg</td>
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<tr>
<td>DASH II Overall Comb. Low Na+</td>
<td>-8.9 mmHg*</td>
<td>-4.5 mmHg*</td>
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<td>vs. Control High Na+ Diet</td>
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<tr>
<td>DASH II Hypertensive Pts. Comb. Low Na+ DASH Diet</td>
<td>-11.5 mmHg*</td>
<td>-6.8 mmHg*</td>
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<tr>
<td>vs. Control High Na+ Diet</td>
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* = p < 0.001

NEJM 1997; 336: 1117-24
NEJM 2001; 344: 3-10
Sodium (Na⁺) Restriction

- Average US intake: 5000 mg/day (Range 3,000-20,000 mg)
- Minimal requirement: 500 mg/day
- Increase Na⁺ intake = Increase BP (E,O,C) and CVD, CVA, LVH, CHD, MI, Death, CRI, AC, Platelet Function, SNS, especially salt sensitive
- Decrease Na⁺ intake = Decrease BP (E,O,C), especially salt sensitive and LRH. Caution in HRH….may increase BP.
- Magnitude BP reduction directly proportional to decrease Na⁺: 150 mmol → 100 mmol → 50 mmol: 4-6 mmHg / 2-3 mmHg

Sodium, endothelial cells and salt sensitivity

- Sodium promotes cutaneous lymphangiogenesis, increases endothelial cell stiffness, reduces size, surface area, volume, cytoskeleton, deformability and pliability, reduces eNOS and NO production and increases TGF-β. This is increased in the presence of aldosterone which mimics these same pathophysiologic changes.
- Both dietary sodium and potassium promote functional changes in the vasculature and lymphatic system independent of BP changes. Potassium counteracts all the actions of sodium.
- Estimated that 51% of hypertensive patients are salt sensitive and 33% are salt resistant.

Sodium and AT 2 Mediated Vasodilatation

- High sodium intake specifically abolishes the AT2-mediated vasodilation, immediately via decreased level of AT2 receptor protein and after 30 days is associated with the abolition of endothelial vasodilation.
- Loss of the AT2 mediated vasodilation increases BP and risk of stroke and CVD.

Salt-Induced hemodynamic regulation is mediated by nitric oxide

- Excess NaCl intake impairs vasodilation and increases vasoconstriction which reduces blood flow and increases BP in both normal and hypertensive patients with or without salt sensitivity.
- Decrease eNOS and NO
- Increased ADMA
- Increased oxidative stress
- Imbalance of NO and A-II
- Endothelial cells act as vascular salt sensors

Potassium, Hypertension and CVD

- Dietary potassium lowers BP in normotensives and hypertensives in a dose related response
- 600 mg K reduces SBP 1.0 mm and DBP .52 mm Hg
- Response depends on race (B>W), sodium, magnesium and calcium intake. Higher sodium intake results in more BP reduction with potassium.
- 4.7 gms (120mmol) of potassium lowers BP 8.0/4.1 mm Hg with reduction in CVA 15 % and MI 11%
- Lowers risk of CVA, CHD, MI, CHF, LVH, CVD, CRI, DM, arrhythmias.
- Reduction in CVA is both BP dependent and non BP dependent.
SODIUM TO POTASSIUM RATIO
PRACTICAL RECOMMENDATIONS
Archives Int Med 2011;171:1183

- Reduce sodium intake to 1500-2000 mg per day
- Increase potassium intake to 5 grams per day
- This gives a K/Na ratio of 2.5-3.3/1.
- Each 1000 mg increase in Na intake per day increases all cause mortality 20%
- Each 1000 mg increase in K intake per day reduces all cause mortality 20%
- Highest quartile of Na/K ratio increased CVD and total mortality by 46% compared to the lowest quartile.

Urinary Sodium and Potassium Excretion and Risk of Cardiovascular Events
JAMA 2011;306:2229

- J shaped curve for sodium excretion and CV events
- Sodium excretion over 7 grams per day or less than 3 grams per day was associated with increased risk of CV mortality and hospitalization for CHF over 56 months.
  - Over 8 grams: CV death 53%, MI 34%, stroke 48% and CHF 51% increase
  - Less than 3 grams: CV death 19%, CHF 23% increase
- Higher potassium excretion was associated with a reduced risk of stroke:
  - 1.5-1.99 grams: 23% RRR
  - 2.0-2.49 grams: 27% RRR
  - 2.5-3 grams: 29% RRR
  - over 3 grams: 32% RRR

Magnesium (Mg++)
Houston MC J of Clinical Hypertension 2011;13:309

- 91 patients in DBPC Trial given 485 mg Mg++ aspartate-HCL
  - BP 2.7/3.4 mm Hg (p<0.18 SBP) (p<0.003 DBP) Maximum is 5.6/2.8 mmHg. Numerous randomized and observational data.
- Effective in HBP, Acute MI, Atherosclerosis, DM, dyslipidemia, LVH and IR
- Intake of 500-1000 mg/day of chelated Mg. (Malate).
  - Measure RBC Mg++
- Milk (Mg++, K+, Ca++) better than Mg++ alone to ↓BP
- Direct vasodilator: Natural CCB, regulates intracellular Ca++, Na+, K+, pH, increase PGE1, Nitric oxide, improves ED and IR.
- Best with high K, low Na intake and taurine to decrease BP
- Enhances effects of anti-hypertensive drugs
  

Protein

- Observational epidemiologic studies indicate a high protein intake reduces BP (non-animal > vs animal protein) in numerous populations. However, cured meat increases BP.
- Low Protein and Low Omega 3 FA intake are associated with higher BP.
- Daily intake recommended 1.0 to 1.5 grams/kg/day depending on many factors.
- Intersalt Study:
  - 10,020 subjects, worldwide had lower BP (3.0/2.5 mm Hg) with dietary protein >30% above mean vs those 30% below mean (81 gms vs 44 gms/day) This is especially true in the elderly and hypertensive patients.
- Mechanisms:
  - ACEI, reduce SNS (EPI, NE), natriuresis, inhibit tyrosine kinase (ERK-MAPK), reduce VSMH, reduce superoxide ion (O2-), reduce aldosterone

SOY PROTEIN
Am J Clin Nutr 2005;81:1012

- Soybean protein 40 grams per day in 302 Chinese adults ages 35-64 years.
  - DB, RCCT for 12 weeks
- Prehypertension and stage 1 hypertension
  - BP reduction net difference: 4.3 mmHg/2.1 mmHg (significant at p<0.05)
  - Effects seen at week 6
- Improves arterial compliance, PPAR agonist, ACEI, reduces SNS activity, atriuretic, reduces tyrosine kinase, VSMH, superoxide anion, reduces aldosterone and improves lipid profile
- Fermented soy is recommended at 30-40 grams per day
- Similar findings in Intersalt and Intermap Trials.
- Large study of 45,864 Chinese women BP associated with soy protein at 25 grams per day. Maximum reduction of BP was 4.9/2.2 mm Hg lower over 3 years.
- Studies show variable results: no change to 7-10% reductions.
**Sardine Muscle (Valyl-Tyrosine): Protein**

- 3 gms of Valyl-Tyrosine for 4 weeks in hypertensive patients reduced BP 9.7 / 5.3 mmHg
- Vegetable drink with sardine protein hydrolysates of Valyl-Tyrosine dipeptide in 13 weeks reduced BP 8/5 mm Hg.
- Valyl-Tyrosine is ACEI: ↓ Ang-II, ↓ Aldosterone
- No Adverse effects

*J Human Hypertens 2000; 14:519-23*
*Fukuoka Igaku Zasshi 2002; 93:208*

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**Whey Protein**

- Significant reduction in BP in animal and human studies
- Must be hydrolyzed to be effective. Rich in bioactive peptides with ACEI activity.
- Act as ACEI
  - IC 50 = .45 mg / ml for BioZate-1
  - IC 50 = 376 mg / ml nonhydrolyzed whey protein
  - IC 50 = 1.3 x 10^-6 for captopril
- 30 grams of hydrolyzed whey protein per day reduced BP 11 / 7 mm Hg in humans within 7 days
- 20 gms of hydrolyzed Whey Protein significantly reduced BP 8/5 mm Hg in 30 patients in 6 weeks.

*J Dairy Sci 2006; 83:355-263*
*J Clin Hypertens 2006; 8: 775*
*Cardiovasc Drugs 2002;16:68*

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**Peptides from Milk Protein**

- Milk proteins, both caseins and whey proteins are a rich source of ACE inhibitory peptides that significantly reduce BP
- Val-Pro-Pro and Ile-Pro-Pro from Lactobacillus helveticus in fermented milk given at 12 gms per day for 4 weeks significantly reduced BP 11.2/6.5 mm Hg
- Extracts of VPP or IPP at 5 to 60 mg per day
- Pooled data: BP reduced 4.8/2.2 mm Hg
- Recent meta-analysis 2010 did not show significant reductions in BP.

*J of Clinical Hypertension 2010;12:153*
*J of Nutrition 2004;134:980S*
*Current Opinion in Lipidology 2010;21:58*

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**BONITO PROTEIN (Sarda Orientalis) and Marine Collagen Peptides**

- Natural ACEI with numerous ACE-inhibitory peptides
- From the tuna/mackeral family
- Bonita Protein reduces BP 10.2/7 mm Hg in humans over 1-3 months.
- Dose: 1.5 grams per day
- No adverse effects and cost effective

*Cardiovasc Drugs 2002;16:68*
*Curr Pharm Dis 2009;15:362*

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**Omega-3 PUFA and Blood Pressure**

- Fish 3 x / week lowers BP (Herring, Haddock, Atlantic Salmon, Trout)
- DHA better to ↓ BP. Use 3-4 grams of DHA with EPA per day with a ratio of 3 parts EPA to 2 parts DHA.
- Lowers BP 8/5 mmHg and reduces HR 6 beats per minute. 24 hr ABM inversely correlates with RBC omega 3 FA content. Improved Cardiac Function, reduce CHF, improve BP and diastolic dysfunction
- Improved Endothelial Dysfunction, increase eNOS and NO
- Reduced plasma norepinephrine and improved insulin sensitivity
- Change Calcium Flux, natural CCB
- Suppress ACE activity and reduce A-II levels
- SUPPRESS TGF-B EXPRESSION
  - Activate Parasympathetic nervous system, nutrition 1998; 14: 627-33
  - Am J Hypertension 2011 July 14 epub
- Reduce MAU and improve renal function

*Current Atherosclerosis Reports 2000; 2: 598-15*
*Hypertension 1999; 34: 253-60*
*Activate Parasympathetic nervous system, nutrition 1998; 14: 627-33*
*Supp. BM 1995; 125: 911-15*
*Hypertension 2007; 50:113 Net Rev 2010; 50:867*
*Am J Hypertension 2011 July 14 epub*
*Atherosclerosis 2011; 212: 187*

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**Omega-3 PUFA :Renal Function and Proteinuria**

In patients with CKD, 4 grams of Omega 3 FA reduced BP 3.3/2.9 mm Hg and HR 4 bpm and TG 24 %

Reduces proteinuria and preserves renal function

*Current Atherosclerosis Reports 2000; 2: 598-15*
*International J Interactive Med 2000; 2: 6-12*
*NEJM 1999; 320: 1037-43*
*Hypertension 1998; 32: 710-17; Am J Clin Nutr 1999; 70: 817-25*
*J of Hypertens 2009; 27: 1061*
**Inflammation Reduction: Omega 3 FA**

- Regulation of transcription factors
- Production of three and five series eicosanoids
- Inflammation resolving lipid mediators
- Suppression of acute phase reactants
- Decrease TNF alpha, IL-1B, IL-6, IL-8, CRP, SAA, PPAR alpha, gamma, RXR, two and four series eicosanoids, monocyte infiltration, MCP-1, VCAM-1, ICAM-1, E-selectin, NFkB activation, platelet aggregation
- Increase three and five series eicosanoids, lipoxins, resolvins and protectins
- Improve cell membrane composition and fluidity

**Diagnosis of Omega 3 FA**

- Omega 3 index of 8% or higher has been reported to be associated with greatest cardio-protection
- Omega 3 index of less than 4% gives the least cardio-protection

**MUFA (Olive Products and Nuts)**

- 23 hypertensive subjects in DBRCo study for 6 months. Extra virgin olive oil vs sunflower oil
- Significant Reduction in BP 8 / 6 mmHg in HBP patients (p <0.05 and <0.01) on 30 to 40 grams per day (3-4 tablespoons)
- Reduces need for antihypertensive drugs in 48% of HBP patients vs 4% in control (p <0.005)
- Reduces BP in Type-2 DM (Clinic and 24 hr ABM)
- Oleic acid, polyphenols. Reduces ox LDL (decrease AT1R stimulation.

**Virgin Olive Oil Reduces Blood Pressure**

- DBRCo crossover study 31 hypertensive elderly patients
- Virgin olive oil (VOO) vs. sunflower oil (SFO) for 4 weeks then 4 week wash out with 4 week crossover.
- SBP reduced to 136 mm Hg with VOO vs 150 mm Hg with SFO (p<0.01)

**Garlic**

- Consistent dose dependent BP reduction in 10 controlled clinical trials was 8 to 10/7-8 mm Hg (Average 8.4/7.3 mm Hg in hypertensive patients.
- Cultivated garlic = Allium Sativum . Not all garlic preparations same
- Wild uncultivated garlic = Allium Urisinum (Bear Garlic), fresh at 1 – 4 cloves / d (5 grams)
- High Adenosin, magnesium, flavonoids, sulfur, allicin, phosphorous and alenes
- High Gamma-Glutamyl Peptides (ACEI’s).
- Natural ACEI and CCB. Increase NO , bradykinin, lower SVR
- Reduces NE sensitivity, ROS, Txax2, improves arterial compliance

**Garlic**

- DBRCP Study of 50 subjects with hypertension
- 900mg aged garlic with 2.4 mg S allylcysteine per day
- 12 weeks
- BP reduced SBP 10.2 mm Hg in patients with SBP over 140 mm Hg ( p< 0.03)
- Need 10,000 mcg of allicin per day to have significant BP lowering effect. This is the amount in four cloves (5 grams) of garlic
**Seaweed**

- **Wakame (Undaria Pinnatifida)**
  - Most popular edible seaweed in Japan
  - ACEi activity similar to Captopril in ↓ BP in SHR
  - ↓ BP in hypertensive patients
    - ↓ SBP 14 ± 3 mmHg and ↓ DBP (5 ± 2 mm Hg) (p <0.01)
    - 3.3 gms dried Wakame
    - 4 weeks study

  - **J Nutr Biochem 2000; 11: 450-4**
  - **J Jpn Soc Clin Nutr 1998; 20: 92**

- **Ion exchange sodium-absorbing / potassium releasing seaweed preparation**
  - 12-24 grams/day for 4 weeks
  - ↓ MAP 11.2 mm Hg (p <0.001) salt-sensitive subjects
  - ↓ MAP 5.7 mm Hg (p <0.05) salt-insensitive subjects
  - BP reduction correlated with PRA

  - **J Nutr Biochem 2000; 11: 450-4**
  - **J Agric FoodChem 2002; 50: 6245**
  - **J Jpn Soc Clin Nutr 1998; 20: 92**
  - **Am J Hypertens 1991; 4: 483**
  - **Ann Nutr Metab 2002; 446: 259**

**Vitamin C**

**Hypertension 2000;35:936 J of Hypertens 1996;14:503**
**J Clin Biochem Nutr 2007;40:141**
**Arzneimittelforschung 2006;56:535 J Chiropr Med 2006;5:60**

- Composite of all clinical trials show average reduction in BP of 7/4 mm Hg with Vitamin C at 250 mg bid to serum level of 100 microgram/L.
- BP response dependent on pretreatment BP
- SBP and 24 hr ABM show best response
- Multiple mechanisms will be discussed
- Enhances activity of CCB and other BP drugs
- Improves BP in elderly resistant hypertensive patients

**Vitamin C : Conclusions**

- SBP, DBP and HR are inversely correlated with Vitamin C intake and plasma ascorbate levels in humans in epidemiologic, observational, cross sectional and controlled prospective clinical trials
- The higher the initial BP, the greater the response
- SBP reduced more than DBP. Improves aortic compliance
- 24 hour ABM shows daytime > nighttime decrease in BP
- BP reduction improved with concomitant use of other antioxidants such as vitamin E, lipoic acid, selenium, etc.
- Improves anti-hypertensive effects of amloidipine
- Lowers BP significantly in elderly hypertensive patients with refractory hypertension and decreases CRP, 8-isoprostane and MDA. 600 mg per day over 6 months lowered BP by 20/16 mm Hg.

**Vitamin C : Conclusions**

- **Mechanisms**: diuretic, improves ED, AC, arterial and aortic collagen, elasticity, antioxidant, open VSM K channels, increase cGMP, recycle E and GSH, anti-inflammatory (LT), anti-thrombotic, anti-lipid, increase NO and PGI, reduces MDA, adrenal steroids, aldehydes neuropeptide peptides and intracellular calcium, improve sympathetic / parasympathetic tone increase in RBC Na/K ATPase and SOD, improves FMD, PWV and AI .
- Decreases binding affinity to AT1 receptor by disruption of disulfide bridges (Am J. Hypertension 2008;21:67-71)
- **DOSE**: 500 qd to BID to serum level of 100 umol/L
EFFECT OF VITAMIN E ON BP IN TYPE 2 DM

- 58 type 2 DM with controlled hypertension in R, DB, PC trial over 6 weeks.
- 500 mg/day of RRR alpha tocopherol or mixed tocopherols with 60% gamma, 25% delta and 15% alpha tocopherols.
- Baseline BP was 130/76 mm Hg. Monitored with 24 hour ABM.
- Patients remained on BP, lipid and DM meds.
- RRR alpha tocopherol: SBP increased by 7 mm Hg (p<0.0001) and DBP increased 5.3 mm Hg (p<0.0001) and increased HR by 2 b/min (p<0.005)
- Mixed tocopherol: SBP increased 6.8 mm Hg (p<0.0001), DBP increased 3.6 mm Hg (p<0.0001) and HR increased 1.8 mm Hg (p<0.01)
- Both treatments reduced plasma F_2 isoprostanes but not urinary F_2 isoprotanes.
- No effects by either treatment on endothelial-dependent or independent vasodilation.
- Vitamin E is metabolized by CYP 450 enzymes (3A4 and 4F2) and may interfere with anti-hypertensive drug metabolism.

Prevalence of Hypertension in Vitamin D deficiency

- 20% incidence at Vit D over 40 ng/ml
- 27% incidence at 30-39 ng/ml
- 41% incidence at 15-29 ng/ml
- 52% incidence at below 15 ng/ml

Vitamin D

- Hypertension: Vitamin D levels below 30 ng/ml have higher circulating levels of PRA and A-II, blunted plasma renal flow and higher BP (52% vs 20%) incidence in lowest vs highest quartile serum Vit D3. (Forman et al, JCH abstract page A 122 PO 298 May, 2010)
- Cardiovascular Disease: CHD, contractility, LVH, VSMH, CHF, diastolic dysfunction, PAD and arrhythmias. Am J Cardiol 2010;106:963
- Insulin resistance, metabolic syndrome, beta cells function and diabetes mellitus.
- Immune Function and infections.
- Lipid Metabolism: Increase large HDL, decrease oxLDL (AT1R stimulation decreased) (J Clin Lipidology 2010;4:413)
- Replacement of Vitamin D with or without a deficiency reduces BP in animals and humans.
- BP reduced about 3.6 to 6.2/3.1 mm Hg but up to 13.1/7.2 mm Hg in Pfeifer female study. Best with unactivated forms of Vitamin D.
- Dose and serum level dependent. Only lowers BP in hypertensive patients.
- Markedly suppresses renin transcription by a VDR-mediated mechanism which regulates electrolytes, volume and blood pressure. Vitamin D binds to VDR then to retinoid X receptor then to DNA to alter gene expression.
- BP reduction is inversely proportional to pretreatment plasma level of 25 OH D. Active 1,25 dihydroxyvitamin D signals through the Vitamin D receptor and provides vascular protection and reduces BP.
- Lowest to highest deciles of plasma 25 OH D have 1.6 to 2.3 times risk of incident hypertension
- Dose: 5000 IU per day depending on many factors. 100 IU of Vitamin D3 increases serum levels by 1ng/ml
- Plasma level to about 55 ng/ml with range of 50 to 80 ng/ml as optimal (to convert ng/ml to nmol/L multiply by 2.5)
- PTH is suppressed at levels of over 30 ng/ml
- Lower HR, PRA, A-II, VSMH, increase NO, improves IR, reduces CAC

References:
- Recent Pat Cardiovasc Dis 2011;6:345
- Hypertension 2007;49:1063
- Ann Intern Med 2010;152:30
**Vitamin B-6 (Pyridoxine)**

- Low vitamin B-6 levels are associated with hypertension in animals and humans
- Co-factor in neurotransmitter and hormone biosynthesis (NE, EPI, serotonin, GABA, kynurenine)
- B-6 increases cysteine synthesis from methionine
  - Cysteine is precursor of glutathione (antioxidant)
  - Cysteine neutralizes aldehydes and increases excretion
- Glutathione neutralizes aldehydes and increases excretion

**References**
- Aybak, Arzneimittel FORSCHUNG 1995;45:1271

**Vitamin B-6**

- **Aybak, Arzneimittelforschung 1995;45:1271**
  - 20 hypertensive subjects vs normotensive controls
  - Vitamin B-6 at 5 mg/kg/day for 4 weeks
    - Decrease SBP 14 mm Hg p <0.001
    - Decrease DBP 10 mm Hg p <0.005
  - Plasma NE (p <0.005)
  - Plasma EPI (p <0.05)
  - Vitamin B-6 is a CAA, CCB, diuretic and improves insulin resistance
  - Dose: 200 mg QD (short term up to 500 mg QD)

**References**
- Am J Clin Nutr 2005;81: 611
- Arch Intern Med 2007;167:626
- J of Clin Hypertension 2007;9:647
- JAMA 2007;298:49
- BMC 2010;8:39
- Am J Hypertension 2010;23:97

**Caffeine and Coffee**

- Cytochrome P-450 - CPY1A2 genotype modifies the association between coffee intake and the risk of hypertension and CVD in a linear relationship.
- Rapid metabolizers IA/IA allele have lower BP and lower risk of MI. For hypertension 36 to 88 RR. BP decreased by 9 mm Hg. About 40% of the population.
- Slow metabolizers IF/IA allele have higher BP 8.1/5.7 mm Hg lasting over 3 hours after consumption of coffee, increased risk of MI, tachycardia, increase aortic stiffness and increased catecholamines .For hypertension 1.72 to 3.00 RR. About 60% of population.
- Polyphenols, chlorogenic acid and dihydrocaffeic acid increase eNOS, improve ED and lower BP about 10/7 mm Hg at 140 mg per day.

**References**
- J of Hypertension 2009;27:1594
- Am J Clin Nutr 2007;86:457
- European J Clinical Nutrition 2007;61:796
- Am J Clin Nutr 2011;94:1113

**Lycopene**

- 30 subjects with Grade I HBP, age 40 – 65
- Tomato lycopene extract for 8 weeks
  - SBP fell 9 mm Hg (p < 0.01)
  - DBP fell 7 mm Hg (p < 0.01)
- Improves anti-hypertensive effect of ACEI, CCB, diuretics by additional 10/5 mm Hg which correlated with plasma lycopene levels.

**References**
- Am Heart J. 2006;1151:100
- Cardiovasc Drugs Ther.2009;23:145
CoEnzyme Q-10 (Ubiquinone)
Rosenfeldt FL. J Hum Hypertens 2007;21:297

- Reduced SVR and BP correlated with increase serum CoQ-10 level (+0.97 µg/ml) (p <0.02) and pretreatment CoQ 10 levels.
- Office BP reductions average 17/10 mm Hg
- Meta-analysis of 12 trials with 362 patients Range BP 11-17/8-10 mm Hg
- Therapeutic plasma levels are 3.0 ng /ml
- Decrease HR 5 beats per minute
- BP effects occurs at 4 to 12 weeks
- BP effects are gone at 7-10 days after discontinuation

Deficiency of Co Enzyme Q-10 in 39% of hypertensive patients vs. 6% of control patients
- Reduced with age, disease, oxidative stress, statins, HLP, CHD, HBP DM, aerobic exercise, atherosclerosis
- Reduces dose and number of BP medications
- Best BP reduction with lowest initial CoQ-10
- Dose: 200 – 400 mg /day (3-5 mg /kg ) Nanoparticle formulation with enhanced absorption

Meta-analysis of 12 trials with 362 patients  Range BP 11-17/8-10 mm Hg

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Atherosclerosis 1997; 129:119-26

CO-Q-10: BURKE STUDY
ISOLATED SYSTOLIC HYPERTENSION
SNJ 2001;94: 1112-1117

- 12 WEEK R, DB P CONTROLLED TRIAL FOR 12 WEEKS IN 83 MEN AND WOMEN WITH ISH (165/81-82MM HG)
- 60 MG CO-Q-10 BID(QGEL)
- INCREASED SERUM CO-Q-10 LEVELS BY 2.2 UG/ML(P<0.01)
- SBP REDUCED 18 MM HG(P<0.01)
- DBP REDUCED 2.6 MM HG(NS)
- 55% RESPONDED AND 45% DID NOT RESPOND : DEFINED AS REDUCTION IN SBP OF >4 MM HG. IN THE RESPONDERS THE AVERAGE REDUCTION IN SBP WAS 26 MM HG.
- LOW ADVERSE EFFECTS (6%)
**Alpha Lipoic Acid**

**Mechanisms of Action**
- Inhibits release and translocation of NF-KB from cytoplasm into nucleus of cell which decreases controlled gene transcription and regulation of endothelin-I, Tissue Factor, VCAM-1
- Improves ED through beneficial effects on NO, AGE’s Vitamin-C and E, glutathione, cysteine, endothelin, Tissue Factor, VCAM-1, Linoleic and myristic acid
- Reduces monocyte binding to endothelium (VCAM-1)
- Increases linoelic acid and reduce myristic acid
- R-Lipoic is best at 100-200 mg per day with biotin 2-4 mg/day

**Alpha Lipoic Acid**

**Mechanism : Vascular Biology**

- ALA
  - Excess Aldehydes Reduced
  - L-Type Ca++ Channel Closes
  - Decreases Cytosolic Ca++
  - Decrease SVR
  - Decrease BP

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**Arginine**

**J of Hypertension 2010;28;S 56**
- Precursor along with endogenous methylarginines for NO via eNOS
- Circulating arginine in plasma in both healthy and patients with vascular disease is 30 fold higher that the Michaelis-Menton constant values for eNOS. This uncoupling leads to production of ROS.
- Oral tetrahydrobipterin improves BP, cardiac function and LVH
- VINTAGE MI study showed arginine did not improve cardiac function post MI and may increase mortality (JAMA 2006;295:58 (low tetrahydrobiopterin, ROS, uncoupling?)

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**L-Arginine (NO Precursor)**

- Reduces BP in humans with acute parenteral and chronic oral administration in Normotensives, Hypertensives, Salt sensitive hypertensives, Hyperlipidmic and DM patients
- In CHD it increases CA blood flow and decreases angina
- In PAD it increases peripheral Blood flow and reduces claudication

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**Meta-analysis of Arginine and Blood Pressure Randomized, Double Blind and Placebo-Controlled Clinical Trials**

- 11 trials with 387 subjects
- Oral arginine 4 to 24 grams a day orally
- Duration of 4 weeks or less
- On no anti-hypertensive medications
- Inverse relationship between baseline BP and response (NS)
- BP reduction 5.39/2.66 mm Hg (p<0.001)
**Taurine**

- **Clinical Use:** HBP, HLP, arrhythmias, CHD, CHF, ASCVD
- **SHR:**
  - ↓ BP 20-25%
  - ↑ proteinuria, ↑ renal Kallikrein
  - ↓ LVH
  - ↓ Uepi + Udopamine
  - ↓ SNS activity centrally
- **Human Studies:** Fujita. Circulation 1987;75:525
  - 19 hypertensive subjects
  - 6 grams taurine x 7 days
  - ↓ BP 9/4.1 mm Hg (p <0.05)
- **Mechanisms:**
  - diuresis, ↑ Una¹, ↓ SVR,
  - ↑ ANF, ↓ homocysteine,
  - ↑ insulin sens., ↓ SNS activity, improves Acetyl Choline responsiveness, ↑ Na⁺ space, adenosine receptor
  - opiates-mediated, improves NO/ED vasodepressor response,
  - ↑ renal Kallikrein, ↓ PRA, lowers A-II, increases kinins, decreases intracellular Ca and Na
  - ↓ aldosterone CNS glycine response and beta receptors
- **Dose:** 3 grams BID

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**PYCNOGENOL**

- Pyconogenol at 200 mg per day in 11 subjects for 8 weeks in placebo, DB, R, Crossover Trial
- Reduced SBP 7 mm Hg (p < 0.05)
- Reduced DBP 2 mm Hg (NS)
- Serum thromboxane B2 levels reduced (P < 0.05)
- Cell membrane protection from oxidative stress
- Increase nitric oxide and improves ED, decrease ET-1
- ACEI action
- Increases Vitamin C levels
- Reduced need for ACEI by 50%

*Nutrition Research* 2001; 21:1251-1260

*Nutrition Research* 2005; 28:315

*Life Sci.* 2004; 74: 855


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**RESVERATROL AND CENTRAL BLOOD PRESSURE**

*Am. J. Hypertens* 2005; 18: 1161

- Subjects given 250 ml of regular or dealcoholized red wine for 2 days and wave reflections with AI, augmentation index and central and peripheral blood pressures measured.
- AI decreased 10.5% with regular red wine and 6.1% with dealcoholized red wine
- No change in peripheral BP
- Central BP reduced by 7.4 mm Hg with regular red wine (p=0.05) and 5.4 mm Hg with dealcoholized red wine. (p=0.019)

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**Resveratrol Improves ED in patients with Metabolic Syndrome**

*Nutrition Research* 2011;31:842-47

- Improves ED(FMD) in patients with metabolic syndrome on both lifestyle treatment or on medications such as ACEI, ARB and statins. Suggests additive mechanism
- No changes in BP, insulin resistance, lipid profile or inflammatory markers.
- Trans resveratrol at 100 mg per day
- SIRT 1 stimulation increases eNOS expression by deacetylation of both lysine 496 and 506
- Also activates Nrf2 to increase oxidative defense and reduce oxidative stress.

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**Resveratrol**

*Blood Pressure* 2010;19:196

- Increases flow mediated vasodilation
- Improves endothelial dysfunction
- Prevents uncoupling of eNOS
- Lowers blood pressure
- Decreases insulin resistance
- Increases adiponectin which reduces vascular inflammation
- Reduces HS CRP
- Decreased LVH
- Blocks effects of A-II
- Induces mitochondrial biogenesis for cardiac remodeling
Beta Blockers reduce melatonin secretion. Measures include GPCR on Mell a and Mell b receptors in autonomic mechanisms AND pineal melatonin secretion.

Melatonin action is by GPCR on Mell-a and Mell-b receptors on autonomic mechanisms AND pineal melatonin secretion.

The normal circadian rhythm of melatonin is a modulator of blood pressure in humans. Mediated in part by GABA(A) receptors and inhibition of plasma A-II levels.

Melatonin levels are reduced by shorted sleep cycle of less than 6 hours, shift work, age, brief light exposure after darkness, trespass light, Beta Blockers, benzodiazepines.

- Natural ACEI. Reduces activity by 36%
- Rich in tannins, anthocyanins and polyphenols.
- Lowers BP in humans by 5% to 12% (p<0.01)
- Reduces carotid IMT by 30% in one year
- Increases nitric oxide, improves ED and lowers BP.
- 150 mg to 300 mg GSE reduced BP 11/8 mm Hg in 4 weeks (p< 0.05)

- In a DB, R, PC, XO study, chronic administration (3 weeks) of melatonin at 2.5 mg one hour before bedtime in hypertensive men, on no anti-hypertensive medications lowered nocturnal BP by 6/4 mm Hg, reduced day-night amplitudes of SBP 15% and DBP 25%, HR same, improved sleep, reduced cortisol levels.
- Endogenous circadian pacemaker in the SCN (supra-chiasmatic nucleus) regulates 24 biological rhythms by endocrine and nervous system mechanisms.
- Hypertensive patients have altered circadian function with blunted day-night sympathetic and parasympathetic tone, reduced vasodilation, suppressed nocturnal melatonin levels due to three neurotransmitters that are reduced by over 50%.
- Measure Urinary 6-hydroxymelatonin sulphate
- Beta Blockers reduce melatonin secretion
- Improves nocturnal dipping response

Grape Seed Extract (GSE)

- High phenolic content in seeds (70% of total grape) activates PI3K/Akt signaling pathway through a redox sensitive mechanism resulting in phosphorylation of eNOS
- Increases nitric oxide, improves ED and lowers BP.

- Melatonin Human BP Studies
  - Improves nocturnal dipping
  - Lowers cortisol
  - Average reduction in all clinical trials on 3-5 mg at night is 6/3 mm Hg.
  - Additive with ARB
  - Mechanisms include GPCR on Mell-a and Mell-b receptors in vascular tissue, binds calmodulin, GABA receptors, inhibits A-II, increase NO and improves ED. Anti-oxidant.
  - Beta blockers reduce melatonin secretion.
**Sesame**

*J Nutr Sci Vitaminol. 2009 55:87*

*J Med Food 2006;9:408*

*Mol Cancer Res 2010;8:751*

*Yale J Biol Med 2006;79:19*

*Nutr J 2011;10:82*

- 60 mg of Sesamin for 4 weeks in mild hypertensive patients by 3.5/1.9 mm Hg (p<0.04)
- Black sesame meal 2.52 grams per day over 4 weeks in 15 subjects reduced SBP 8.3 mm Hg (p< 0.05).
- Additive with nifedipine
- Lowers glucose, HbA1C, TG and LDL-C
- Also suppresses NF-kappa B which reduces inflammation
- Active ingredients are sesamin, sesamolin, sesaminol glucosides and furofuran lignans

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**OXIDATIVE STRESS, GLUTATHIONE, GLUTATHIONE PEROXIDASE, HYPERTENSION AND CHD**

*Circulation 2004; 109:544-549*

- Increased Glutathione Peroxidase (GSH-Px) lowers BP, reduces MI, LVH and CHF.
- GSH-Px confers more cell, tissue and organ protection than SOD or catalase, or the combination of both.
- 5 GSH-Px (#1-#4 are selenium-dependent, #5 is not) is located in mitochondria and cytosol, which neutralize lipid peroxides and hydrogen peroxide, preventing formation of hydroxyl radical and other ROS. GSH-Px has greater affinity for hydrogen peroxide than catalase.
- Peroxiredoxins (Prx) (#1-#6) scavenge hydrogen peroxide as well. Prx #3 is in the mitochondria and protects cardiac muscle.
- Highest quartile of RBC GSH-Px had 71% lower risk of MI compared to lowest quartile (p<.001). GSH-Px is major CHD risk factor (NEJM 2003; 349:1605-13). Abnormal genotypes also exist which increases risk (Coronary Artery Disease 2003; 14:149-153).

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**Combination Therapy**

**Nutrient-Nutrient**

- Sesame with beta blocker, diuretic and nifedipine
- Pycnogenol with ACEI
- Lycopene with various anti-hypertensive agents
- R lipoic acid with ACEI
- Vitamin C with CCB
- NAC with Arginine
- Garlic with ACEI, diuretic and beta blocker
- Co-enzyme Q 10 with ACEI and CCB

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**Anti-hypertensive drug – nutrient interactions**

*Handbook of Food Drug Interactions CRC press 2003*

*Therapeutic Advances in Cardiovascular Disease 2010;4:165*

- **Diuretics:**
  - Decrease K, Mg, phosphorus, sodium, chloride, folate, B6, zinc, iodine and Co Q 10
  - Increase homocysteine, calcium, glucose, insulin resistance, type 2 DM and creatinine with renal insufficiency.
- **Beta Blockers** decrease CoQ 10
- **ACEI and ARB** decrease zinc

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**Plasma Renin Activity (PRA)**

*J of Hypertension 2011;29:2276*

*NEJM 1993;329:918*

*Am Heart J 2011;162:585-96*

High PRA is associated with greater risk of:

1. Myocardial infarction and ischemic heart disease
2. Stroke
3. Congestive heart failure
4. Chronic kidney disease
5. Total cardiovascular disease and mortality
6. Total mortality

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**SELECTION OF ANTI-HYPERTENSIVE TREATMENT BASED ON BLOOD PRESSURE STRATIFICATION USING RENIN PROFILING PLASMA RENIN ACTIVITY (PRA)**

*N Engl J Med 1972;286:441-449*

*Am Heart J 2011;162:585*

- **Low Renin Hypertension (LRH):** Increased Intravascular Volume (Volume dependent)
  - PRA < 0.65 ng/ml/hr 30% of patients
- **High Renin Hypertension (HRH):** Decreased Intravascular Volume
  - PRA > 0.65 ng/ml/hr 70% of patients
- **Very high Renin Volume Depleted:** PRA > 6.5 ng/ml/hr
Plasma Renin Activity and Aldosterone

**ARR: Aldosterone Renin ratio**
- ARR over 80 is LRH
- ARR over 40 is probably LRH
- ARR less than 10 is HRH
- ARR between 10 and 40: not sure

Measurement of PRA and Serum Aldosterone

- Random ambulatory serum levels of plasma renin activity (PRA) and serum aldosterone
- Most accurate in drug naïve patients
- Does not require alterations in patient position, time of day, sodium intake etc.
- Levels will be altered by concomitant anti-hypertensive medications which requires more sophisticated interpretation.

Selection of Antihypertensive Treatment Based on Blood Pressure Stratification Using Renin Profiling (Plasma Renin Activity: Laragh Method)

**Treatment Selection**

- **Low Renin Hypertension (LRH):** Volume Drugs and Nutraceuticals: Calcium Channel Blockers (CCB), Diuretics, Serum Aldosterone receptor antagonists like Spironolactone and Epleronone (SARA), alpha blockers
- **High Renin Hypertension (HRH):** RAS or Renin Drugs and Nutraceuticals: Angiotensin Converting Enzyme Inhibitors (ACEI), Angiotensin Receptor Blockers (ARB), Direct Renin Inhibitors (DRI), Beta Blockers (BB), Central Alpha Agonists (CAA)

Nutrient Testing

1. Determine nutrient deficiencies that contribute to the hypertension and vascular disease. Recommend: Micronutrient analysis MNT measures lymphocyte intracellular nutrient analysis for previous 6 months.
2. Replace nutrient deficiencies and re-evaluate at 3 months.
3. Initiate therapeutic nutritional program
4. Initiate therapeutic nutritional supplement program with vitamins, antioxidants, minerals and nutraceuticals. May take 3 to 6 months to achieve maximal effect compared to drug therapy, but long-term BP reductions may be very similar.

Hypertension Institute Clinical Research Trial on Nutrition and Nutraceuticals in Hypertension

Houston, NC. Journal of Therapeutic Advances in Cardiovascular Disease. The role of cellular micronutrient analysis and minerals in the prevention and treatment of hypertension and cardiovascular disease 2010; 4:165-83

- 671 hypertensive patients with BP of 140/90 to 210/115 diastolic at baseline
- FIA of micronutrients and PRA were done in all patients
- Treatment was with antihypertensive drugs, repletion of nutritional deficiencies, therapeutic doses of appropriate nutritional supplements, DASH 2 diet, combined aerobic and resistance exercise and ideal body weight and composition.
- Composite nutritional program included VasculoSirt, EFA Sirt Supreme, ResveraSirt-HP and CardioSirt-BP
Hypertensive patients had significantly more micronutrient deficiencies compared to normal patients ($n=2667$) $p<0.0017$ Bonferroni method.

These included biotin, serine, asparagine, calcium and vitamin D ($p<0.0017$) and for B1, choline, insulin, magnesium, CoQ 10, lipoic acid, and total antioxidant level with Spectrox ($p<0.05$).

Repeat testing at 6 months showed significantly improved antioxidant profile by $8.47\%$ ($p=0.03$) and over $97\%$ complete repletion rate of micronutrients.

62% of the hypertensive patients over a period of 6 months (average) range 4-12 months were able to completely taper and discontinue anti-hypertensive drugs with controlled BP of 120/80 mm Hg to 126/84 mm Hg.

The economic implications are large. US expenditure on anti-hypertensive drugs is about 20 billion per year (10% of US expenditure on drugs).

Drug costs alone using this program could be decreased by about 12.4 billion dollars per year.

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 and it may take longer to work than the antihypertensive drug, when used in combination with other nutrients and nutraceuticals, the antihypertensive effect is magnified.

These natural compounds are divided into the major antihypertensive drug classes such as diuretics, beta blockers, central alpha agonists, CCB, ACEI,ARB’s and DRI’s.
Natural Antihypertensive Compounds Categorized by Antihypertensive Class

- **Beta Blockers (BB)**
  - Hawthorne Berry

- **Central Alpha Agonists (CCA)** (Reduced SNS Activity)
  - Taurine
  - K⁺
  - Zinc
  - Na⁺ Restriction
  - Protein
  - Fiber

- **Flavoids**
  - Vitamin C
  - Vitamin E
  - Coenzyme Q-10
  - L-Arginine
  - Taurine
  - Celery
  - Garlic

Nutrients and Nutraceuticals with Calcium Channel Blocking (CCB) Activity

- **Alpha Lipoic Acid (ALA)**
- Magnesium (Mg++)
- Vitamin B-6 (Pyridoxine)
- Vitamin C
- Vitamin E: high gamma/delta E with alpha tocopherol, (↑ cytosolic Mg++ with ↓ Ca++), also diuretic
- N-Acetyl Cysteine (NAC)
- Hawthorne
- Celery
- Omega-3 fatty acids (EPA + DHA)
- Calcium
- Garlic
- Taurine

Summary and Conclusions

- Vascular Biology (ED and AC) plays a primary role in the initiation and perpetuation of hypertension, CVD and TOD
- Nutrient-gene interactions are a predominant factor in promoting beneficial or detrimental effects in cardiovascular health and hypertension
Summary and Conclusions

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

- Oxidative stress, inflammation and immunologic reactions initiate and propagates hypertension and cardiovascular disease.

- 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 micronutrient will prevent and treat hypertension and CVD.

Summary and Conclusions

- There is a scientifically proven role for selected use of single and component nutraceuticals, vitamins, antioxidants and minerals in the treatment of hypertension based on controlled human studies that are additive to optimal nutrition and other lifestyle modifications.

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

Contact Information

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**Book Ordering Information**

- **What Your Doctor May Not Tell You About Hypertension**: order from Hachett Book Group 237 Park Ave. NY, NY
  Phone 212-364-1428 or fax 1800-477-5925
- **Handbook of Hypertension by Blackwell/Wiley**: order from online at [www.wiley.com](http://www.wiley.com) or call 877-762-2974
- **What Your Doctor May Not Tell You About Heart Disease**: Available February 2012. Grand Central Publishing NY, NY. (Hachett Books)

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**CASE 1**

- 42 yo BM with hypertension for 10 years
- BP 160/100 mm Hg on no meds.
- Normal weight, Non smoker
- No caffeine or alcohol use
- History negative
- PE shows mild hypertensive retinopathy, S3 gallop, systolic murmur
- Lab is normal except for FBS of 102 mg % and Vitamin D level of 24 ng/ml. HSCRP is 1.0 (normal)
- EKG : Left ventricular hypertrophy
- Plasma renin activity (PRA): 3.2 pg/ml/hr
- MNT micronutrient deficiencies: Mg, CoQ 10, Vitamin D, Vitamin C and Vitamin B 6

What is your treatment plan?

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**Audience Response Questions CASE 1**

1. This patient has what type of hypertension
   a. Low renin hypertension
   b. High renin hypertension
   c. Cannot determine from the data
   d. It does not matter in regards to treatment

2. The best initial treatment is
   a. Replacement of all micronutrient deficiencies and start recommended high dose therapy with CoQ 10, Vitamin B 6 and whey protein.
   b. DASH diet with supervised exercise program
   c. Diuretic and Beta Blocker therapy
   d. A and B
   e. None of the above

3. This patient also has which of the following:
   a. Metabolic Syndrome
   b. Inflammatory vascular disease
   c. Insulin resistance
   d. None of the above

4. The diagnosis above is due to
   a. Obesity
   b. High intake of protein and fish
   c. Multiple micronutrient deficiencies
   d. None of the above

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**Case 1 Discussion**

- Patient has high renin hypertension (HRH) and should be treated with, nutrition, nutraceuticals, exercise initially and integrate drugs depending on BP response and TOD, that work in HRH such as ACEI, ARB or DRI.
- Replete all measured deficiencies: Mg, Coq 10, Vitamin C, Vitamin B 6 and Vitamin D.
- Omega 3 FA: Natural ACEI and CCB, lowers glucose
- GLA : Natural ARB
- Whey Protein: Natural ACEI
- Vitamin C: Natural ARB also
- CoQ 10 : Natural ARB also
- Mg: Natural CCB also
- Vitamin B 6: Natural ARB also
- Vitamin D: reduces PRA and good treatment for HRH.
Case I Treatment and Results
- DASH 2 diet
- 60 minutes of combined ABCT exercise per day
- Magnesium chelates 500 mg twice per day
- Co Q 10 100 mg twice per day to blood level of 3 ug/ml
- Vitamin B 6 100 mg twice per day
- Vitamin C 500 mg twice a day
- EFA (Omega 3 complex): (DHA, EPA, GLA, gamma delta E): 5 grams per day
- Hydrolyzed whey protein: 30 grams per day
- Vitamin D 3 10,000 IU per day to blood level 60 ng/ml

RESULTS: BP at 6 weeks: 134/88 mm Hg
BP at 3 months: 124/82 mm Hg
FBS 94 mg %, no murmur, retinopathy improved.

Case 2
- 55 yo WF with new onset hypertension
- BP 148/94 mm Hg on no medications or supplements
- History negative
- PE normal
- Lab normal
- EKG normal
- PRA 0.20 ng/ml/hr
- MNT deficiencies: GLA, lipoic acid, vitamin B6 and magnesium.
- Omega 3 index is low at 2. (normal is over 8)
- What is your treatment?

Audience Response Questions CASE 2
1. What type of hypertension does this patient have?
   a. Low renin hypertension
   b. High renin hypertension
   c. Normal renin hypertension
   d. Very high renin hypertension

2. What is the best type of treatment for this patient?
   a. No treatment, patient is a low risk for CVD
   b. Immediate treatment with ACEI or ARB
   c. Replete micronutrients and start high dose nutrients that treat the mechanism of hypertension based on the PRA status.
   d. Start high sodium and low potassium diet to induce the desired diuretic effect.

3. Name 4 micronutrients that would be best treatment options
   a. Bonito protein, whey protein, hawthorne berry and pycnogenol
   b. Omega 3 FA, vitamin B 6, R- lipoic acid (with biotin) and magnesium.
   c. Either A or B will work in this patient
   d. None of the above.

4. How long should you wait until rechecking the MNT micronutrient deficiency and omega 3 deficiency?
   a. One year
   b. 3 months
   c. 2 weeks
   d. No need to check again

Case 2 Discussion
- Patient has low renin hypertension (LRH)
- Use nutraceuticals and/or drugs that work in LRH such as diuretics and calcium channel blockers (CCB)
- Replete deficiencies: GLA, lipoic acid, vitamin B 6 and magnesium
- GLA is also natural diuretic
- Lipoic acid is also natural CCB
- Vitamin B 6 is natural CCB and diuretic
- Taurine is natural diuretic
- Magnesium is natural CCB and diuretic
- Omega 3 fatty acids are natural CCB. The balanced EFA omega 3 complex also has GLA and gamma/delta tocopherol with diuretic effects

Case 2 Treatment and Results
- Dash 2 Diet
- Combined aerobic and resistance exercise at 6 days per week at 60 minutes per session (ABCT)
- GLA 500 mg twice per day
- R-lipoic acid 100 mg per day with Biotin 2 mg per day
- Vitamin B 6 at 100 mg twice per day
- Taurine at 3 grams twice per day. Lowers BP and is diuretic
- Magnesium chelates at 500 mg twice per day
- EFA Omega 3 complex 5 grams per day

RESULTS: BP at 6 weeks: 126/84 mm Hg
BP at 3 months: 118/78 mm Hg
Case 3

- 42 yo WM with Hypertension for 10 years treated with a diuretic (HCTZ 25 mg a day) and Beta Blocker (metoprolol 100 mg per day).
- BP is 176/104 mm Hg
- Complains of fatigue, dyspnea, ED, poor memory
- PE: 5'8" wt is 196 lbs, retinopathy, systolic murmur, bradycardia at 48 b/min
- Lab: LDL cholesterol 142 mg %, dense with 1250 LDL-P, TG 340 mg %, HDL 32 mg % and FBS is 106 mg %, PRA is 0.10 ng/ml/hr, K is 3.5 mg % and Mg is 1.0 mg%
- MNT deficiencies: CoQ 10 and glutathione
- EKG: bradycardia, Left atrial and left ventricular hypertrophy, unifocal PVC's
- ECHO: mitral insufficiency 2 +, LAH and LVH
- CAPWA: low C2 AC at 3.2 (normal >7)
- ENDOPAT: moderate endothelial dysfunction (1.32) (normal > 1.68)
- What is your Treatment?

Case 3 Treatment

- DASH 2 Diet
- Combined exercise at 60 minutes per day
- Weight loss to IBW of 153 lbs
- Taper metoprolol over 6 weeks
- Taper HCTZ over 6 weeks
- Start CoQ 10 100 mg twice per day
- Why? protein at 30 grams per day, Niacinamide 1000 mg per day, NAC 1000 mg per day, and lipoic acid 1000 mg to increase glutathione
- Increase potassium in diet to 5000 mg per day
- Magnesium Chelates 1000 mg twice per day
- RESULTS: BP at 2 weeks: 145/93 mm Hg
  BP at 4 weeks: 132/86 mm Hg
  BP at 8 weeks: 122/83 mm Hg HR 68 b/min
  BP at 4 months: 118/76 mm Hg

4 months: Off all prescription meds, weight is 164 lbs, no dyspnea, ED or fatigue, memory normal. Feels well. LDL is 102 mg %, with normal HDL and LDL. HDL 40 mg %, LDL 108 mg %, FBS 88 mg %. Murmurs absent, retinopathy improved, no PVCs
- PRA: 0.16 ng/ml/hr off all drugs. LRH
- CAPWA: C2 7.6
- ENDOPAT: No endothelial dysfunction
- ECHO: LAH decreased. No mitral insufficiency

Case 3 Major Points

- Type of hypertension can not be determined with PRA as BB decrease PRA and diuretics increase PRA.
- Replete nutrient deficiencies and electrolyte deficiencies: CoQ10, glutathione, K+ and Mg++
- BP poorly controlled on two BP meds with side effects. Will need to taper and discontinue both drugs and start new treatment
- Fatigue from BB and diuretic
- Dyspnea from BB
- ED from BB and diuretic
- Poor memory from BB
- Bradycardia from BB
- Obesity is exacerbated by BB
- Dyslipidemia from BB and diuretic
- Dysglycemia from BB and diuretic
- Hypokalemia and hypomagnesiemia from diuretic
- Low CoQ10 from BB and diuretic
- Low CAPWA and ED from BP, BB and diuretic