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Review Article

Treatment of Cardiovascular Disease with Nutritional Supplements

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Abstract

We have reached a limit in our ability to reduce the incidence of Coronary Heart Disease (CHD), Congestive Heart Failure (CHF) and Cardiovascular Disease (CVD) utilizing the traditional evaluation, prevention, and treatment strategies for the top 5 cardiovascular risk factors – hypertension, diabetes mellitus, dyslipidemia, obesity and smoking. Statistics show that approximately 50% of patients continue to have CHD or Myocardial Infarction (MI) despite "normal" levels of these five risk factors as traditionally defined. A more logical and in depth understanding of these top five risk factors is necessary. Advanced testing should include 24 hour ambulatory blood pressure monitoring, advanced lipid profiles, dysglycemic parameters, visceral obesity with effects of adipokines and evaluation of the three finite vascular endothelial responses of inflammation, oxidative stress and immune vascular dysfunction. Congestive heart failure is most commonly due to CHD and presents with both systolic and diastolic heart failure. Understanding translational cardiovascular medicine allows appropriate correlation of the CHD risk factors to the presence or absence of vascular injury and disease utilizing non -invasive vascular testing. This provides for early identification, prevention and treatment of CHD, CHF and CVD.

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Introduction

Cardiovascular medicine needs a complete functional and metabolic medicine reevaluation related to diagnosis, prevention and integrative treatments. We have reached a limit in our ability to reduce CVD and CHD [1]. The cardiovascular system is literarily "on fire" Our present treatments are not always effective in reducing this vascular inflammation. CVD, CHD and CHF remain the number one cause of morbidity and mortality in the United States [2]. Statistics show that we spend approximately $80 billion a year treating CVD alone [2] and over 2200 US citizens die from stroke or MI each day [2-5]. CHD includes angina, MI, ischemic heart disease, ischemic cardiomyopathy with both systolic (low ejection fraction) and diastolic congestive heart failure (normal ejection fraction with stiff and non- compliant left ventricle. The most common cause of CHF in the US is ischemic heart disease.

The traditional evaluation, prevention, and treatment strategies for the top 5 cardiovascular risk factors – hypertension, diabetes mellitus, dyslipidemia, obesity, and smoking, have resulted in what is now referred to as a "CHD gap". Statistics show that approximately 50% of patients continue to have CHD or Myocardial Infarction (MI) despite "normal" levels of these five risk factors as traditionally defined. We maintain a cholesterol-centric approach to the management of CHD but do not address the basic etiologies of CHD such as inflammation, oxidative stress and immune vascular dysfunction. However, there are important details within each of these top 5 risk factors that are not being measured by physicians and are thus ignored in the prevention and treatment of CHD [2]. In fact, there are at least 395 other risk factors that physicians either do not know about, ignore or do not use appropriate techniques to identify and treat them. In order to truly revolutionize the treatment of CVD, new therapies will need to involve management of the pathophysiologic risk factors, mediators and their downstream effects, as well as the finite vascular responses. This will be achievable by using a combination of targeted personalized treatments with genomics, proteomics, metabolomics, nutrition, nutraceutical supplements, vitamins, minerals, anti-oxidants, anti-inflammatory agents, anti-immunological agents, and pharmacologic agents. Future studies must begin to measure all of the pertinent risk factors that have been reviewed here to correlate their direct relationship with CHD. Only by addressing all of these factors will we be able to decrease or halt subsequent vascular aging, damage and CVD. Thus, it is imperative that we utilize other methods to prevent and treat CVD.

Revolutionizing the treatment of cardiovascular disease

The blood vessel has three finite responses to an infinite number of insults [2]. Those responses are inflammation, oxidative stress, and vascular immune dysfunction. Tracking backwards from those 3 finite responses brings us to the genesis of CVD with the goal of starting effective treatments to resolve the downstream abnormalities,

Cell membrane physiology and cell membrane dysfunction are keys to this treatment strategy. This membrane barrier separates the outside and the inside of every cell. This includes

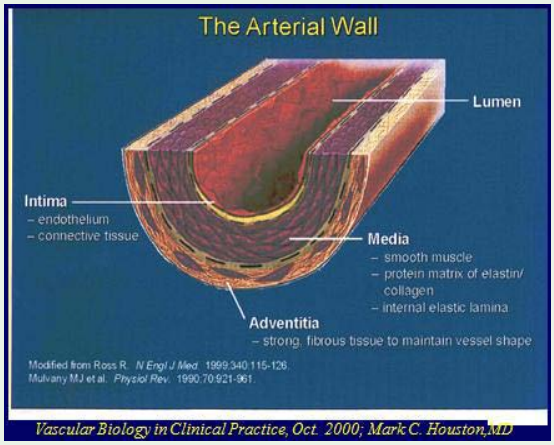

Figure 1: The arterial wall includes the endothelium with connective tissue (intima), the media or vascular smooth muscle and the adventitia with supporting fibrous tissue.

the endothelium, enterocyte, the blood brain barrier, or any other membrane. Membrane activation determines all of the signaling mechanisms that occur from the external to the internal milieu and the downstream internal cell signal pathways [2].

Any cell membrane insult such as high blood pressure, LDL cholesterol, glucose, microbes, toxins, heavy metals or homocysteine results in a reaction diffusion wave throughout the cell membrane that disrupts the signaling mechanisms and induces membrane damage and dysfunction [6,7]. One small insult becomes a heightened response (metabolic memory) to create further cell damage [6,7]. The blood vessel is really an innocent bystander in a correct but often a chronic and deregulated vascular response to these infinite insults.

In the acute setting, any vascular insult results in a correct defensive response by the endothelium. The vascular immune dysfunction, oxidative stress or inflammatory responses are usually short-lived, appropriate, and regulated [2]. However, chronic insults result in a chronic exaggerated and dysregulated vascular dysfunction with preclinical then clinical CVD due to maladaptation of various systems such as the. Renin-Angiotensin-Aldosterone (RAAS) system, Sympathetic Nervous System (SNS) and others [2].

Most diseases are arbitrarily defined with a specific abnormal level of some test or measurement. Hypertension is defined as greater than 140/90 mmHg, dyslipidemia as an LDL-cholesterol is over 100 mg/dL, and glucose intolerance as a fasting glucose over 99 mg/dL [2]. However, it is very clear that there exists a continuum of risk starting at lower levels of BP, LDL cholesterol and glucose as well as for most other CHD risk factors [2]. For example, we know that the blood pressure risk for CVD actually starts at 110/70 mmHg, and that LDL-cholesterol reduces nitric oxide in the endothelium at 60 mg/dL and fasting glucose risk starts at 75mg/dL is the level at which CHD risk begins [2]. There is a progressive continuum of risk with all of the CVD risk factors and mediators that effect the blood vessel, leading initially to functional abnormalities (endothelial dysfunction), then to structural abnormalities of the vascular and cardiac muscle (stiffness and hypertrophy) and to preclinical and clinical CVD.

Finally, it is important to understand the concept of "translational vascular medicine. Do the risk factors that are measured actually translate into a vascular illness? Does the absence of those risk factors actually define vascular health? Functional and structural markers of vascular and endothelial dysfunction are not always used to predict risk to identify the vascular effects of CHD risk factors or the presence of vascular disease. Risk factor scoring systems such as Framingham, American Heart Association, and American College of Cardiology or COSEHC (Consortium of Southeastern Hypertension Centers) are used to predict risk. We assume that if a patient has risk factors, they also have vascular disease; but if they don't, they may have vascular health. It is important to measure sensitive indicators of endothelial dysfunction and vascular structural disease that are induced by the insults. Early detection with aggressive treatment will reduce CVD.

The endothelium, endothelial function, and endothelial dysfunction

The endothelium is a very thin monolayer of vascular cells which forms an interface between the circulating luminal blood and the vascular smooth muscle [2,4,8] (Figure 1).

Endothelial dysfunction results in inflammation, oxidative stress, immune dysfunction, abnormal growth, vasoconstriction, increased permeability, thrombosis and ultimately CVD [2,4,8,9]. The ENDOPAT non invasive vascular testing is the most validated method to assess endothelial dysfunction. The ENDOPAT coupled with 24 hour ABM and advanced lipid testing will correlate early vascular disease to the underlying pathophysiology.

(Figure 2) illustrates LDL-cholesterol's role in atherosclerotic plaque formation [10]. LDL-cholesterol becomes modified in the sub endothelial layer and susceptible to oxidation, glycation and acetylation [10]. Higher LDL particle number (LDL-P) and small dense LDL increase the risk for LDL modification and CHD. The modified LDL is consumed by scavenger receptors (SR-A and CD-36) on macrophages to form foam cells. Foam cells lead fatty streaks and plaque formation. There are over 38 different steps in this process that can be treated to disrupt the dyslipidemia- induced vascular disease [10].

Vascular disease is a balance of vascular injury (angiotensin II and endothelin), vascular protection with nitric oxide coupled with vascular repair that includes endothelial progenitor cells (EPCs)

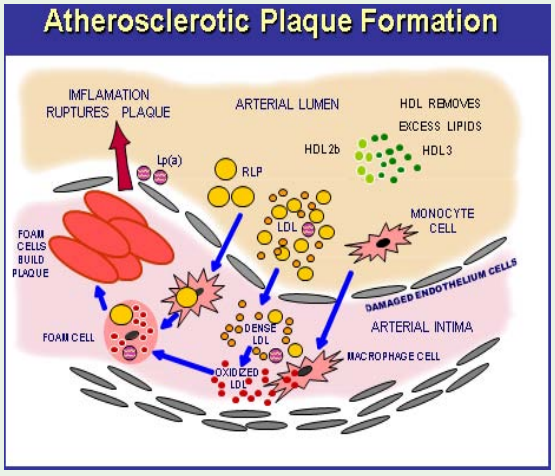

Figure 2: Simplified illustration of atherosclerotic plaque formation.

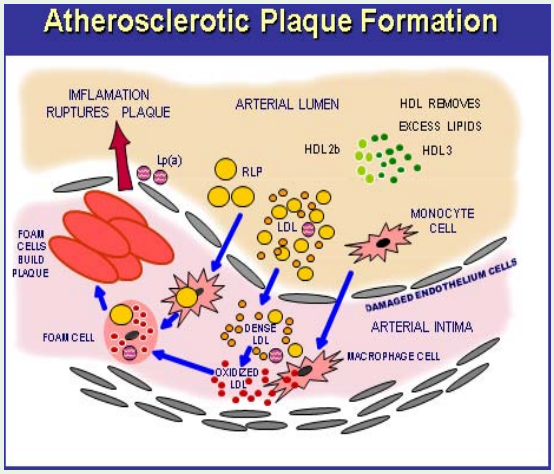

Figure 3: The endothelium is subject to an infinite number of insults but can only elicit a finite number of responses to those insults.

produced in the bone marrow [2,4]. The infinite insults result in preconditioned and heightened "metabolic memory" responses that trigger the3 finite downstream responses which have a bi-directional communication involving endothelial dysfunction, vascular smooth muscle dysfunction and cardiac dysfunction [4,6]. Once endothelial dysfunction has developed, a smaller insult occurring at a later time can result in a heightened response that induces more vascular damage [4,6].

The pathophysiology of vascular disease

- Oxidative stress with Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) are increased in the arteries and kidneys and with a decreased oxidative defense;
- Inflammation is increased in the vasculature and kidneys with increased High Sensitivity C-Reactive Protein (HS-CRP), leukocytosis, increased neutrophils and decreased lymphocytes and increased activity of the Renin–Angiotensin–Aldosterone System (RAAS).
- Autoimmune dysfunction of the arteries and kidneys occurs with increased White Blood Count (WBC), and involvement of CD4+ (T-helper cells) and CD 8+ (cytotoxic T-cells).

These insults result in abnormal vascular biology with endothelial dysfunction and cardiac and vascular smooth muscle hypertrophy and dysfunction. Of course, nutragenomics, genetics and epigenetics also play a role in the pathophysiology of vascular disease [3].

(Figure 3) offers an insight into the infinite insults that bombard the endothelium. The infinite insults are divided into 2 major categories: biomechanical (blood pressure, pulse pressure, shear stress, and oscillatory pressure within the arterial system and biochemical (e.g., nutritional and biohumoral factors, microbes, sterile antigens, non -sterile antigens and environmental toxins).Most plaques form at the bifurcation of arteries.

Endothelial cells express various receptors that determine the interaction between the insults and the downstream mediators. These include Pattern Recognition Receptors (PRR), Toll-Like Receptors (TLR), Nod-Like Receptors (NLR), and caveolae [11-14]. The TLRs and NLRs are membrane receptors that react to external insults with appropriate intracellular signaling that usually induces inflammation, oxidative stress and immune dysfunction within the cell. The caveolae are membrane lipid micro domains that when interrupted or stimulated reduce eNOS (endothelial nitric oxide synthase) and nitric oxide levels with an increased BP, inflammation, dyslipidemia, oxidative stress, immune dysfunction and atherosclerosis. The various risk factors and risk mediators attach to one of the receptors in the membrane and then set off a cascade of the three finite responses (inflammation, oxidative stress, and immune dysfunction), which leads to endothelial dysfunction and ultimately CVD [11].

Interrupting the finite pathways

The key to the successful prevention and treatment of CVD is recognition of the risk factors, optimal aggressive and early treatment of the risk factors and identification of treatments that will interrupt the pathways that connect the risk factors to these receptors. The TLR 1, 2 and 4 are the most common of the PRR type TLRs related to the vascular membrane and endothelial dysfunction. The NLRs (NOD 1 and NOD 2) are also type of PRRs that involve the vascular membrane. There are many scientifically proven nutraceuticals and dietary factors that reduce TLR and NLR activation [14]:

- Curcurmin (tumeric): TLR 4, NOD 1 (NLR), and NOD 2 (NLR)
- Cinnamaldehyde (cinnamon): TLR 4
- Sulforaphane (broccoli): TLR 4
- Resveratrol (nutritional supplement, red wine, grapes): TLR 1
- Epigallocatechin gallate (EGCG) (green tea): TLR 1
- Luteolin: celery, green pepper, rosemary, carrots, oregano, oranges, olives: TLR 1
- Quercetin: (tea, apples, onion, tomatoes, capers): TLR 1;
- Omega 3 fatty acids: Interrupt caveolae lipid micro domains TLRs and NODs, decrease inflammation and HS CRP, lower BP, decrease LDL P, increase LDL and HDL size, improve glycation parameters and insulin sensitivity, decrease immune vascular dysfunction, decrease CHD plaque formation, improve CHD and CHF symptoms and outcomes.

The goal is to use a dynamic systems biology, functional and metabolic medicine approach to establish cardiovascular ecology, balance, and all stasis (achieve stability through change) and minimize chronic internal and external cardiovascular stressors, mediators, and risk factors that insult the blood vessel. An attempt should be made to reduce the all static load, prevent, regulate, and treat the "abnormal" downstream finite responses.

The polygenetic codes for CVD identifies 30 separate loci that are associated with MI and CHD, but only a minority of those 30 loci have anything to do with the top 5 cardiovascular risk factors [3]. The majority of those loci deal directly with inflammatory pathways. Evaluation and treatment of only at the top 5 risk factors and how they interact with our genome will never reduce CVD and the CHD gap will persist.

Atherosclerosis, endothelial dysfunction, and vascular disease are post-prandial phenomena [15]. Ingestion of sodium chloride, refined

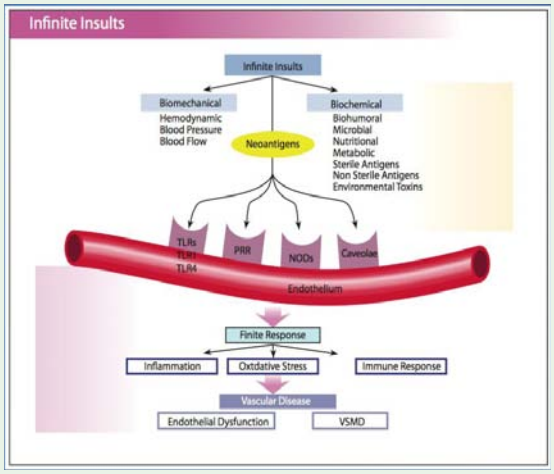

Figure 4: Progression of atherosclerosis from the initial lesion to fatty streak then to atheroma and complicated lesion with plaque formation and subsequent plaque rupture with myocardial infarction.

carbohydrates, and foods containing saturated fats and trans fats, trigger gluco-toxicity, triglyceride toxicity, vascular endotoxemia, inflammation, oxidative stress, and immune dysfunction [6,13,15]. Furthermore, these responses may be perpetuated long after the original insult with a heightened continued inflammatory response (metabolic memory) [6]. Fortunately, studies have shown that eating a diet rich in potassium and magnesium with low-glycemic foods (vegetables, fiber), monounsaturated and polyunsaturated omega 3 fats, polyphenols, and antioxidants can help to prevent post-prandial endothelial dysfunction and reduce future CV events [8-10]. Early evidence of CVD in the form of fatty streaks has been documented in children in the first and second decades of life (Figure 4) [2]. The vascular disease is sub-clinical for 10 to 30 years or more prior to any cardiovascular event [2,4,8]. Endothelial dysfunction is the earliest functional abnormality, followed by changes in arterial compliance, stiffness and elasticity. It is important to begin using technologies that allow earlier identification of cardiovascular dysfunction before any structural changes have occurred.

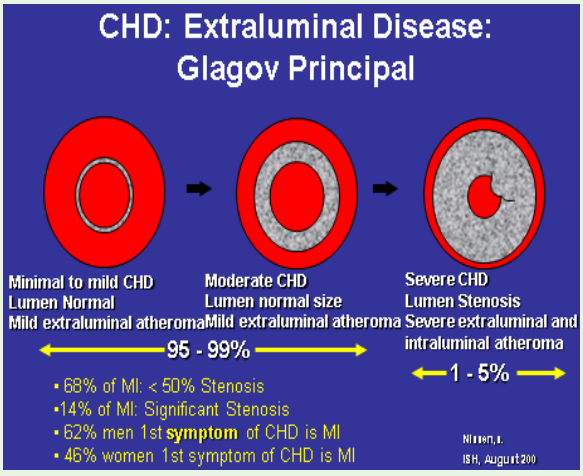

Figure 5: Illustration of the vessel changes that occur as coronary heart disease progresses.

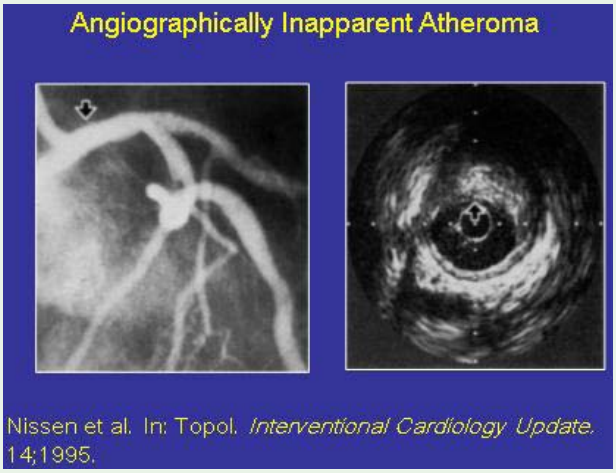

Figure 6: Coronary heart disease that is not detectable by angiogram (left) is clearly evident using computed tomography (right).

Coronary heart disease

(Figure 5) illustrates the vessel changes that occur as CHD progresses. On the left is a fairly normal artery. In the middle, the CHD has progressed from minimal to moderate CHD with the sub endothelium layer becoming thickened but the lumen is still the same size. This extra luminal plaque and inflammation could be seen with computerized CT angiogram (CTA) or Magnetic Resonance Angiogram (MRA) but missed by conventional coronary arteriogram (Figure 6). The image on the right in (Figure 5) there is extensive extra-luminal and intraluminal disease.

Coronary heart disease risk factors

Hypertension: The lack of proper types of imaging, ignoring the majority of the 400 or more CHD risk factors and not properly evaluating the top 5 risk factors are some of the reasons for the persistence of the CHD gap [2]. For example, only a 24 hour ABM (ambulatory blood pressure monitor) can identify specific BP risks for CVD such as nocturnal BP, dipping, non-dipping, BP surges, BP load, white coat and masked hypertension and BP variability. Non dipping is defined as a less than 10% reduction in BP at night compared to daytime. Nocturnal BP is the primary determinate of CVD related to BP measurements. Nocturnal blood pressure is more clinically important than day blood pressure (27/15 mmHg difference is optimal) [8]. The BP load is the number of BP readings over 140/90 mm Hg in 24 hours. The normal BP load is less than 15 % of the total BP readings over 140/90 mm Hg. BP surges that are high and rapid during the early AM hours between 3 and 9 AM as well as labile or variable BP will increase CVD and plaque rupture [8]. Furthermore, morning blood pressure surges (level and rapidity) increase the risk of ischemic stroke, MI, and left ventricular hypertrophy [8]. Excessive dipping is associated with an increased risk of ischemic stroke and reverse dipping is associated with an increased risk of Intracerebral Hemorrhage (ICH). Hypertension is not a disease; it is really a marker for vascular dysfunction. Therefore it is crucial that it is correctly identified. The following points should always be considered when evaluating blood pressure [8]:Normal blood pressure is 120/80 mmHg, but there is a continuum of risk for CVD starting at 110/70 mmHg.

Table 1: Natural Antihypertensive compounds categorized by antihypertensive class [9].

Antihypertensive Therapeutic class (Alphabetical listing)	Foods and ingredients listed by therapeutic class	Nutrients and other supplements listed by therapeutic class
Angiotensin converting enzyme inhibitors	Egg yolk Fish (specific): Bonito, Dried salted fish, Fish sauce Sardine muscle/protein Tuna Garlic Gelatin Hawthorne berry Milk products (specific): Casein Sour milk Whey (hydrolyzed) Sake Sea vegetables (kelp) Sea weed (Wakame) Wheat germ (hydrolyzed) Zein (corn protein)	Melatonin Omega-3 fatty acids Pomegranate Pycnogenol Zinc
Angiotensin receptor blockers	Celery Fiber Garlic MUFA	Coenzyme Q 10 Gamma linolenic acid NAC Oleic acid Resveratrol Potassium Taurine Vitamin C Vitamin B6 (pyridoxine)
Beta blockers	Hawthorne berry	
Calcium channel blockers	Celery Garlic Hawthorn berry MUFA	Alpha lipoic acid Calcium Magnesium N-acetyl cysteine Oleic acid Omega-3 fatty acids: Eicosapentaenoic acid Docosahexaenoic acid Taurine Vitamin B6 Vitamin C Vitamin E
Central alpha agonists (reduce sympathetic nervous system activity)	Celery Fiber Garlic Protein	Coenzyme Q 10 Gamma linolenic acid Potassium Restriction of sodium Taurine Vitamin C Vitamin B6 Zinc
Direct Renin Inhibitors Direct vasodilators	Celery Cooking oils with monounsaturated fats Fiber Garlic MUFA Soy	Vitamin D Alpha linolenic acid Arginine Calcium Flavonoids Magnesium Omega-3 fatty acids Potassium Taurine Vitamin C Vitamin E
Diuretics	Celery Hawthorn berry Protein	Calcium Coenzyme Q 10 Fiber Gamma linolenic acid L-carnitine Magnesium Potassium Taurine Vitamin B6 Vitamin C Vitamin E: high gamma/delta tocopherols and tocotrienols.

Table 2: An integrative approach to the treatment of hypertension [9].

Intervention category	Therapeutic intervention	Daily intake
Diet characteristics	DASH I, DASH II-Na+ or PREMIER diet	Diet type
	Sodium restriction	1500mg
	Potassium	5000mg
	Potassium/sodium ratio	>3:1
	Magnesium	1000mg
	Zinc	50mg
Macronutrients	Protein Total intake from non-animal sources, organic lean or wild animal protein, or coldwater fish	30% of total calories, which 1.5-1.8 gram/ kg body weight
	Whey protein	30 grams
	Soy protein (fermented sources are preferred)	30 grams
	Sardine muscle concentrate extract	3 grams
	Milk peptides (VPP and IPP)	30-60 mg
	Fat	30% of total calories
	Omega-3 fatty acids	2-3 grams
	Omega-6 fatty acids	1 gram
	Omega-9 fatty acids	2-4 tablespoons of olive or nut oil or 10-20 olives
	Saturated fatty acids from wild game, bison, or other lean meat	<10% total calories
	Polyunsaturated to saturated fat ratio	>2.0
	Omega 3 to omega 6 ratio	1.1-1.2
	Synthetic *trans* fatty acids	None (completely remove from diet)
	Nuts in variety	*Ad libidum*
	Carbohydrates as primarily complex carbohydrates and fiber	40% of total calories
	Oatmeal or	60 grams
	Oatbran or	40 grams
	Beta-glucan or	3 grams
	Psyllium	7 grams
Specific foods	Garlic as fresh cloves or aged Kyolicgarlic	4 fresh cloves (4 grams) or 600mg aged garlic taken twice daily
	Sea vegetables, specifically dried wakame	3.0-3.5grams
	Lycopene as tomato products, guava, watermelon, apricots, pink grapefruit, papaya or supplements	10-20mg
	Dark chocolate	100 grams
	Pomegranate juice or seeds	8 ounces or one cup
	Sesame	60 mg sesamin or 2.5 grams sesame meaL
Exercise	Aerobic	20 minutes daily at 4200 KJ/week
	Resistance	40 minutes per day
Weight reduction	Body mass index <25 Waist circumference: <35 inches for women <40 inches for men Total body fat: <22% for women <16% for men	Lose 1-2 pounds per week and increasing the proportion of lean muscle
Other lifestyle recommendations	Alcohol restriction: Among the choice of alcohol red wine is preferred due to its vasoactive phytonutrients.	< 20 grams/day Wine <10 ounces Beer < 24 ounces Liquor <2 ounces
	Caffeine restriction or elimination depending on CYP 450 type	< 100mg/day
	Tobacco and smoking	Stop
Medical considerations	Medications which may increase blood pressure.	Minimize use when possible, such as by using disease-specific nutritional interventions
Supplemental foods and nutrients	Alpha lipoic acid with biotin	100-200 mg twice daily
	Amino acids: Arginine	 5 grams twice daily
	Carnitine	1 to 2 grams twice daily
	Taurine	1 to 3 grams twice daily
	Chlorogenic acids	150-200mg
	Coenzyme Q 10	100mg once to twice daily
	Grape Seed Extract Hawthorne extract	300mg 500 mg twice a day
	Melatonin N acetyl cysteine (NAC) Olive Leaf Extract (oleuropein) Pycnogenol Quercetin	2.5 mg 500 mg twice a day 500 mg twice a day 200 mg 500 mg twice a day
	Resveratrol (*trans*)	250mg
	Vitamin B6	100mg once to twice daily
	Vitamin C	250-500mg twice daily

	Vitamin D3	Dose to raise 25- hydroxyvitamin D serum level to 60ng/ml
	Vitamin E as mixed tocopherols	400 IU

- Each increase of 20/10 mmHg doubles cardiovascular risk.
- Before age 50, the diastolic blood pressure predicts CVD risk best;
- After age 50, the systolic blood pressure predicts CVD risk best;
- 24-hour ambulatory blood pressure monitoring is more accurate than office or home blood pressure measurements and should be the standard of care for defining blood pressure and CVD risk.
- Mercury cuffs are best. Electronic arm cuffs are good. Do not use wrist or finger monitors.
- Blood pressure load: The percent over 140/90 mmHg should be less than 15 % of total BP.
- White coat hypertension (office BP > home BP) and masked hypertension (home BP> office BP).

Nutritional and nutraceutical supplements and other life style changes that improve BP are shown in (Tables 1 and 2) [9].

Coronary heart disease risk factors

Dyslipidemia: Dyslipidemia is another one of the top 5 cardiovascular risk factors. Proper measurement, risk assessment and treatment using advanced lipid profiles is proven and recommended [10-12,16,17] An advanced lipid profile will measure:

- LDL-C total
- LDL-P: LDL particle number (drives CHD risk)
- LDL size (dense type B versus large type A)
- Modified LDL (oxidized, glycated, glyco-oxidized and acetylated)
- Antibodies to oxLDL and modified LDL
- Apolipoprotein (APO) B elevated
- APO B antibodies and immune complexes
- Lp(a)
- HDL-C total
- HDL-P: HDL particle number
- HDL size (large 2b versus small type 3)
- Dysfunctional HDL
- Pro-inflammatory and pro-atherogenic HDL
- Myeloperoxidase (MPO) and dysfunctional APO A
- Low APO A
- Low paraoxonase (PON)-1 and PON-2
- Increased APO-CIII
- Serum free fatty acids
- VLDL and triglyceride (TG) total
- Large VLDL
- VLDL-P particle number
- Remnant particles

The primary driving cardiovascular risk related to LDL-cholesterol is the number of LDL- particle number (LDL-P) and apolipoprotein Bparticles) [10,12]. HDL-P (particle number) is most protective with larger HDL type 2b being a second important protective mechanism [10,12]. Larger number and size of HDL are more efficient at reverse cholesterol transport, cholesterol efflux and more protective to the vascular system in numerous other ways. It is also important to analyze dysfunctional HDL [10,12,16,17]. The loss of HDL function reduces Reverse Cholesterol Transport (RCT) and Cholesterol Efflux Capacity (CEC), reduces oxidative defense, and increases oxidative stress and inflammation. Dysfunctional HDL my represent the most important protective factor of HDL compared to HDL-P or HDL size related to CHD. Patients who have a HDL of 85mg/dL or more often have dysfunctional HDL that is not protective and may be pro-inflammatory or atherogenic [16,17]. VLDL, triglycerides and remnant particles are very atherogenic and thrombogenic [10,12]. Nutritional and Nutraceutical supplements for the treatment of dyslipidemia are shown in (Table 3) [10,12].

Coronary heart disease risk factors

Dysglycemia: A Fasting Blood Sugar (FBS) of over 75 mg increases CHD by 1% per increase of 1 mg/dL, and induces endothelial dysfunction [2]. If a patient has a FBS of 100 mg(often considered a normal level) the risk of CHD is increased by 25% [2] A 2-hour Glucose Tolerance Test (GTT) over 110 mg increases CHD by 2 % per 1 mg/dL increase in glucose [2]. The current definition of an abnormal 2-hour GTT is>140 mg. If a patient's result is140 mg, which again is currently classed as "normal, "CHD and MI are increased by 60%. Hyper insulinemia is also an independent risk factor for CHD [2]. Insulin resistance creates inflammation, reduces nitric oxide levels, causes endothelial dysfunction and vascular disease through the Mitogen Activated Protein Kinase (MAPK) pathway, which is inflammatory and atherogenic and induces hypertension, diabetes mellitur and CVD, as opposed to the phosphatidylinositol 3-kinase (PI3K) pathway, which is anti-inflammatory, anti-hypertensive and anti-atherogenic [2]. It is important to measure all glycation parameters including fasting glucose, 2 hour GTT, insulin levels, C-peptide and proinsulin, depending on the clinical setting [16].

Obesity with increased levels of inflammatory and oxidative stress related adipokines contribute to CHD. Measurement of body weight, waist and hip circumference and waist to hip ratio, BMI and body composition with total body fat and visceral fat with measurement of lean body mass and using Body Impedence Analysis (BIA) will help predict CHD risk [18]. Interval aerobic and resistance exercise should also be part of the comprehensive CHD prevention program.

Non invasive vascular testing

Fortunately, there are a number of non-invasive tests to determine vascular pathology before it actually starts [2]. A discussion of these

Table 3: Nutrition and nutraceutical supplements for the treatment of dyslipidemia [10,12].

• Red yeast rice 2400 to 4800 mg at night with food (lowers LDL)
• Plant sterols 2.5 grams per day. (reduces absorption of cholesterol)
• Berberine 500 mg per day to twice per day. (reduces cholesterol absorption and inhibits HMG COA reductase and PCSK9)
• Niacin (nicotinic acid B3) 500 to 3000 mg per day as tolerated pretreated with quercetin, apples, ASA. Take with food and avoid alcohol. Never interrupt therapy. (lowers TG and increases HDL and HDL function and revserse cholesterol transport)
• Omega-3 fatty acids with EPA/DHA at 3/2 ratio 4 grams/day with GLA at 50% of total EPA and GLA and gamma/delta tocopherol. (reduces TG, increases HDL, decreases LDL P and increases LDL size)
• Gamma delta tocotrienols 200 mg hs. (lowers LDL)
• Aged garlic- Kyolic standardized 600 mg twice per day.(lowers LDL and TG)
• Sesame 40 grams per day (lowers LDL)
• Pantethine 450 mg BID (increase HDL and lowers LDL and TG)
• MUFA 20 to 40 grams per day (EVOO 4 tablespoons per day): reduces oxLDL
• Lycopene 20 mg per day: improves RCT
• Luteolin 10 per day: improves RCT
• Trans resveratrol 250 mg per day: blocks uptake oxLDL by macrophages
• NAC 500 mg twice per day: blocks uptake oxLDL by macrophages
• Carnosine 500 mg twice per day: blocks AGE products
• Citrus bergamot 1000 mg per day: lowers LDL
• Quercetin 500 mg twice per day: reduces inflammation
• Probiotics standardized 15 to 50 billion organisms BID: improves microbiome and lipids
• Curcumin 500-1000 mg twice per day: reduce inflammation
• EGCG 500-1000 mg BID or 60-100 ounces of green tea per day: blocks oxLDL
• Pomegranate one cup of seeds/day or 6 ounces of juice per day. Improves HDL and HDL function.

techniques is beyond the scope of this paper; however the reader is encouraged to find out more about these technologies, particularly Endo PAT, a post-brachial artery study, which is very accurate at assessing endothelial function and diagnosing endothelial dysfunction, Computerized Arterial Pulse Wave Analysis (CAPWA) for endothelial function and arterial compliance, carotid Intimal Medial Thickness (IMT), heart rate variability and heart rate recovery time, ECHO, Magnetic Cardiograph (MCG) and Cardiac CT angiograms for obstructive coronary heart disease and coronary calcium score [2,8,18-21]. The ENDOPAT is the most cost effective and accurate noninvasive test to identify early endothelial dysfunction to predict future CVD and CHD. This test along with 24 hour BP, advanced lipid testing and glycation measurements are the best initial ways to evaluate the CV patient.

Treatment

The prevention and treatment of cardiovascular disease, CHD and CHF require an early and aggressive program that includes optimal nutrition, antioxidants, nutritional supplements, weight management, resistance and aerobic interval exercise programs, tobacco cessation and other life style changes that can be incorporated into a pharmaceutical regimen as necessary.

Endothelial dysfunction

The treatment of hypertension, dyslipidemia, dysglycemia and obesity have been maintaining optimal endothelial function is most important in preventing CHD and future CV events. Maintaining optimal nitric oxide bioavailability is the key in maintaining endothelial function. This involves argentine, nitrates and nitrites, eNOS function (endothelial nitric oxide syntheses) and cofactors such as folate, tetrahydrobiopterin, glutathione, NADH and FADH. Endothelial dysfunction is the first functional abnormality in CVD [22-24]. The Mediterranean diet and DASH diets have been shown to improve endothelial function and reduce CV event rate by about 30 % [20-22] (Table 4). Various supplements such as vitamin D to a blood level of about 60 ng/ml, vitamin C at 250 mg bid, aged garlic 600 mg bid, Quercetin 500 to 1000 mg bid, Cur cumin 500 to 1000 mg bid, Co- enzyme Q 10 to a blood level of 3 ug/ml, lycopene 20 mg per day and various polyphenols, flavonoids, beets and beet root extract and omega 3 fatty acids at 1000 to 5000 mg per day improve eNOS, nitric oxide and endothelial function [22-24] (Table 4).

Coronary heart disease and congestive heart failure

Coronary heart disease, systolic CHF with a low ejection fraction and diastolic CHF can be effectively managed with various supplements as shown in (Table 5). These supplements improve coronary artery endothelial function, reduce oxidative stress, and improve oxidative defense, decrease inflammation and cardiovascular immune dysfunction. They also improve cardiac contractility, ventricular compliance, metabolic and nutritional function of the cardiac myocyte, myocardial bioenergetics, ATP production, oxygen delivery and reduce in cardiac arrhythmias and plaque progression, enhance plaque regression, stabilize plaque and reduce plaque rupture and myocardial infarction, stent restenosis and CABG re-stenosis [25-32] (Table 5).

Table 4: Nutrition and supplements to improve endothelial function.

DASH and Mediterranean diet increase nitric oxide
Vitamin D and C reduce inflammation and immune dysfunction, increase nitric oxide
Aged garlic increase nitric oxide
Quercetin reduces inflammation
Co enzyme Q 10 : antioxidant and reduces oxLDL
Lycopeneimproves RCT
Omega 3 fatty acids increase nitric oxide, improve BP, lipids and glucose
Polyphenols and flavonoids: Cacao, tea, catechis, berry anthocyanins. orange juice and hesperidein, wine polyphenols, beets and beet root extract. All improve nitric oxide and ED
Pomegranate increases HDL and HDL function, improves nitric oxide
Curcumin reduces inflammation
Arginine and citrullene increase nitric oxide
Nitrates and nitrites in dark green leafy vegetables and beets increase nitric oxide
Resveratrol increases nitric oxide
Glutathione : intracellular antioxidant
N-acetyl cysteine: reduces macrophage oxLDL uptake
Lipoic acid; Water and lipid soluble antioxidant
B vitamins improve nitric oxide

Table 5: Coronary heart disease and congestive heart failure.

Summary: Metabolic Cardiology : Non Drug Treatment of Angina, CHD and CHF

- Taurine 3 grams bid
- D-Ribose 5 grams tid or qid
- CoQ 10 300 mg bid
- Magnesium chelates 500-1000 mg bid
- High potassium diet 5000-10,000 mg per day
- Carnitine tartrate 3 grams bid
- R-Lipoic Acid 300-600 mg bid (pyruvate decarboxylase complex)
- Malic Acid 240 mg bid
- Aged Garlic 1200 mg a day
- Curcumin 500 to 1000 mg bid
- Vitamin C 500 mg bid
- Sesame oil 200-300 ml per day
- Carnosine 500 to 1000 mg per day
- Probiotics (Saccharomyces boulardii and others)

Summary: Metabolic Cardiology : Non Drug Treatment of Angina, CHD and CHF

- Vitamin K2 MK 7 150 ug qd
- Omega 3 FA (EFA proprietary product 6 capsules bid 5 grams per day
- Glutathione precursors: NAC 1000 mg bid, R-lipoic acid extended release 300 mg bid, whey protein 40 grams per day, selenium 200 ug/d
- Vitamin D 3 to level of 60 ng/ml
- B Vitamins with at least 200mg thiamine qd
- Zinc 50 mg per day. Check copper levels
- Selenium 200 micrograms per day
- Proprietary vascular product: 5 caps bid
- Trans-Resveratrol (Resvera-Sirt HP) 250 mg qd
- Creatine: 2000 mg per day
- Quercetin 1000 mg bid
- Sauna Treatments

Plaque Stabilization and Reversal and Reduction in Coronary Artery Calcification: Evidenced Based

- Vitamin K2 MK 7 : Menaquinone 100 micrograms/day and MK 4 1000 ug/day
- Omega 3 Fatty acids: 5 gms/day
- Aged Garlic extract (AGE): 600-1200 mg bid
- Curcumin 5000 mg per day
- Vitamin C 1000 mg bid
- Arginine 5000 mg per day
- AGE with statins
- Pomegranate
- Statins
- ACE inhibitors
- ARB's
- DHP-CCB
- HDL

Stent Restenosis

- Vitamin K2 MK 7 : Menaquinone 100 micrograms/day and MK 4 1000 ug/day
- Omega 3 Fatty acids: 5 gms/day
- Aged Garlic extract (AGE): 600-1200 mg bid
- Curcumin 5000 mg per day
- Vitamin C 1000 mg bid
- Arginine 5000 mg per day
- ACE inhibitors
- ARB's

Conclusion

The top 5 cardiovascular risk factors, as they are currently defined, are not an adequate explanation for CHD. In order to close the CHD gap the top 5 risk factors must be better defined and treated while assessing the other 395risk factors and mediators. Early detection and aggressive prevention and treatment of vascular disease are needed before any structural changes occur. New laboratory tests, such as the advanced lipid profiles, 24 hour BP monitoring, and specific tests to identify inflammation, oxidative stress such and immune vascular dysfunction are needed. In addition vascular translational medicine will need to be evaluated with new imaging technologies, such as Endo PAT, CAPWA, carotid IMT, MCG, HRV and CT Angiogram..

In order to truly revolutionize the treatment of CVD, new therapies will need to involve management of the pathophysiologic risk factors, mediators and their downstream effects, as well as the finite vascular responses. This will be achievable by using a combination of targeted personalized treatments with genomics, proteomics, metabolomics, nutrition, nutraceutical supplements, vitamins, minerals, anti-oxidants, anti-inflammatory agents, anti-immunological agents, and pharmacologic agents. Most of the nutritional therapies with supplements will achieve improvement in vascular function within 4 months, as which time re-assessment is indicated. Future studies must begin to measure all of the pertinent risk factors that have been reviewed here to correlate their direct relationship with CHD. Only by addressing all of these factors will we be able to decrease or halt subsequent vascular aging, damage and CVD.

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