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Review Article

New Concepts in the Prevention and Treatment of Coronary Heart Disease

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Abstract

We have reached a limit in our ability to reduce the incidence of Coronary Heart Disease (CHD) 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 is required of these top five risk factors including the evaluation of 24 hour ambulatory blood pressure monitoring, advanced lipid profiles, dysglycemic parameters, visceral obesity with effects ofadipokines and of the three finite vascular endothelial responses which include inflammation, oxidative stress and immune vascular dysfunction to the infinite number of insults. Understanding translational cardiovascular medicine to correlate the CHD risk factors to the presence or absence of vascular injury and disease with non -invasive vascular testing will allow for early identification, prevention and treatment of CHD and CVD.

Keywords: Cardiovascular disease; Hypertension; Dyslipidemia; Inflammation; Oxidative stress; Immune vascular dysfunction

Introduction

Cardiovascular medicine needs a complete functional and metabolic reevaluation related to diagnosis, prevention and integrative treatments. We have reached a limit in our ability to treat cardiovascular disease (CVD) appropriately [1]. The cardiovascular system is literarily "on fire" Our present treatments are not effective in reducing this vascular inflammation.CVDremains the number one cause of morbidity and mortality in the United States [2]. Statistics show that we spend approximately $80 billion a yeartreating CVD alone [2] and over 2200 US citizens die fromstroke 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" [4]. Approximately 50% of patients continue to have CHD or MI despite having "normal" levels of these risk factors as currently defined in the medical literature [2,5]. We maintaina 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 or they are not using appropriate techniques to identify and treat them. Thus, it is imperative that we now begin to examine other methods to prevent and treat CVD[2].

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 between the outside and the inside of every one of our cells such as the endothelium, enterocyte, theblood brain barrier, or any other membrane, determines all of the signaling mechanisms that occur from the external to the internal milieu [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 dysregulated 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

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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. 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 the risk for LDL-cholesterol causing reduction in nitric oxide in the endothelium starts at 60 mg/dL and fasting glucose risk starts at 75mg/dL [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 and topreclinical and clinical CVD.

Finally, it is important to understand the concept of"translational vascular medicine." For example: Do the risk factors that are measured actually translate into a vascular illness? And, vice versa: Does the absence of those risk factors actually define vascular health? At this time we often do not use functional and structural markers of vascular and endothelial dysfunction to identify the vascular effects of CHD risk factors or the presence of vascular disease. Instead, we are relying only upon risk factors or some risk factor scoring system such as Framingham or COSEHC (Consortium of Southeastern Hypertension Centers). 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 lining of vascular cells which forms an interface between the circulating blood in the lumen and the vascular smooth muscle [2,4,8]. When the endothelium is working correctly (endothelial function) all the blood elements and the vascular smooth muscle remain normal. However, when endothelial dysfunction occurs, the results are inflammation, oxidative stress, immune dysfunction, abnormal growth, vasoconstriction, increased permeability, thrombosis andultimately CVD [2,4,8,9s].

Figure 1 illustrates LDL-cholesterol's role in atherosclerotic plaque formation [10]. Once inside the vessel wall LDL-cholesterol becomes susceptible to oxidation and modification by free radicals and glycation [10]. Oxidized-LDL and glycated LDL are toxic to the vessel wall. The modified LDL is consumed by scavenger receptors (SR-A and CD-36) on macrophages to form foam cells. Foam cells are not able to process the oxidized-LDL or modified LDL and continue to accumulate oxidized and modified-LDL forming a plaque which may rupture and cause acute coronary thrombosis.This is the progression that needs to interrupted. There are actually 38 different steps in this process that are important in the treatment of dyslipidemia- induced vascular disease [10].

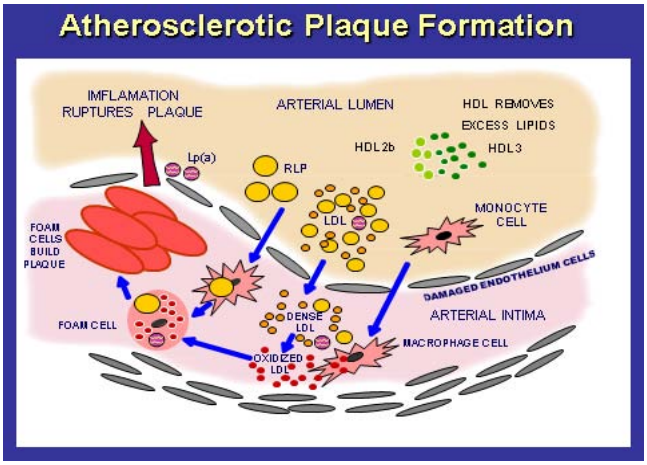

Figure 1: A simplified illustration of atherosclerotic plaque formation.

Vascular disease is a balance of vascular injury (angiotensin II and endothelin) versus vascular repair with endothelial progenitor cells (EPCs), produced in the bone marrow [2,4]. The infinite insults result in preconditioned and heightened "metabolic memory" responses that trigger the 3 finite downstream responses that have a bi-directional communication involving endothelial dysfunction, vascular smooth muscle, and cardiac dysfunction [4,6]. Once endothelial dysfunction has developed, a smaller insult occurring at a latercan result in a heightened response that induces more vascular damage [4,6]. The concept of metabolic memory was demonstrated by Youssef-Elabd et al, who found thatshort-term exposure of adipose cells to uncontrolled levels of saturated fatty acids and glucose lead to a long-term inflammatory insult within adipocytes [6].

The Pathophysiology of Vascular Disease [2,4]

What are the causes of vascular disease? The major causes are:

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

These problems result in abnormal vascular biology with endothelial dysfunction and vascular smoothmuscle hypertrophy and dysfunction. Of course, genetics, genomics, and epigenetics also play a role in the pathophysiology of vascular disease [3].

Figure 2 offers an insight into the infinite insults that the endothelium is bombarded by. The infinite insults are divided into 2 major categories: biomechanical (,blood pressure, pulse pressure, shear stress, and oscillatory pressure within the arterial system – most plaques form at the bifurcation of arteries) and biochemical (e.g.,

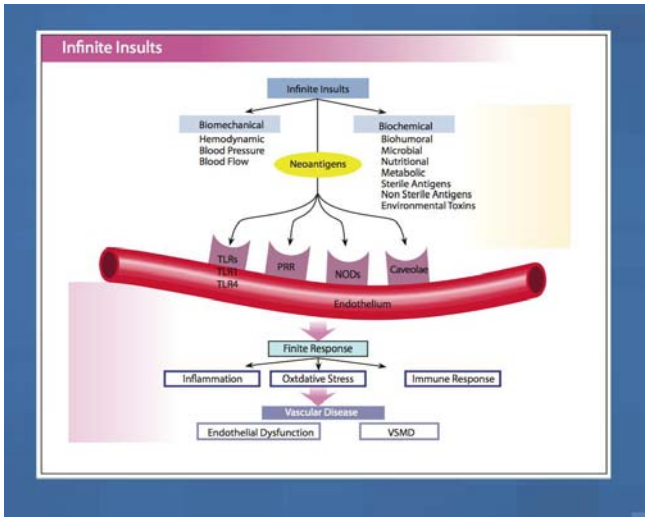

Figure 2: The endothelium is subject to an infinite number of insults but can only elicit a finite number of responses to those insults.

nutritional factors, microbes, sterile antigens, and environmental toxins.)

Endothelial cells express various receptors that determine the interaction between the insults and the downstream mediators. These include Pattern Recognition Receptors (PRP), Toll-Like Receptors (TLR), Nod-Like Receptors (NLR), and caveolae [11]. 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 microdomains that when interrupted or stimulated reduced nitric oxide levels and 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 both recognition 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. The scientifically proven nutraceuticals and dietary factors that accomplish this are listed below [12]:

- Curcurmin (tumeric): TLR 4, NOD 1 (NLR), and NOD 2 (NLR) (these are all PRR) [12]
- Cinnamaldehyde (cinnamon): TLR 4 [12]
- Sulforaphane (broccoli): TLR 4 [12]
- Resveratrol (nutritional supplement, red wine, grapes): TLR 1 [12]
- Epigallocatechin gallate (green tea): TLR 1 [12]

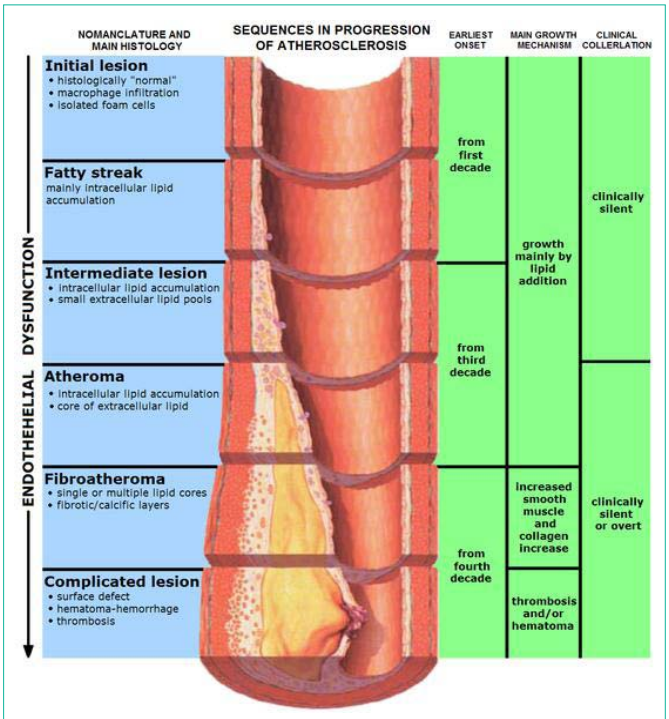

Figure 3: Progression of atherosclerosis.

- Luteolin (celery, green pepper, rosemary, carrots, oregano, oranges, olives: TLR 1 [12]
- Quercetin (tea, apples, onion, tomatoes, capers): TLR 1 [12]
- Chrysin: TLR 1 [12]
- Omega 3 fatty acids: Interrupt caveolae lipid microdomains TLRs and NODs,, decrease inflammation and HS CRP, lower BP, decrease LDL P, increase LDL and HDL size, improve glycation parameters, decrease immune vascular dysfunction, decrease CHD plaque formation, improve CHD and CHF symptoms and outcomes [12].

The goalis touse a systematic (dynamic systems biology), functionaland metabolic medicine approach to establish cardiovascular ecology, balance, and allostasis (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 allostatic 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 has 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 [13]. Ingestion of sodium chloride, refined carbohydrates, and some foods containing trans fats may trigger gluco-toxicity, triglyceride toxicity, vascular endotoxemia,

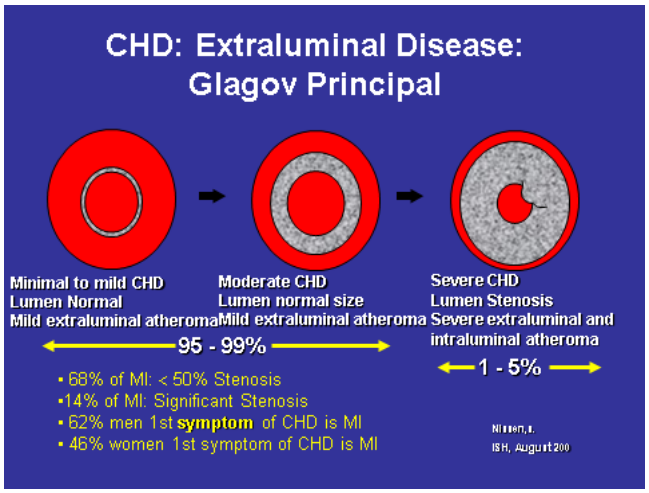

Figure 4: Illustration of the vessel changes that occur as coronary heart disease progresses.

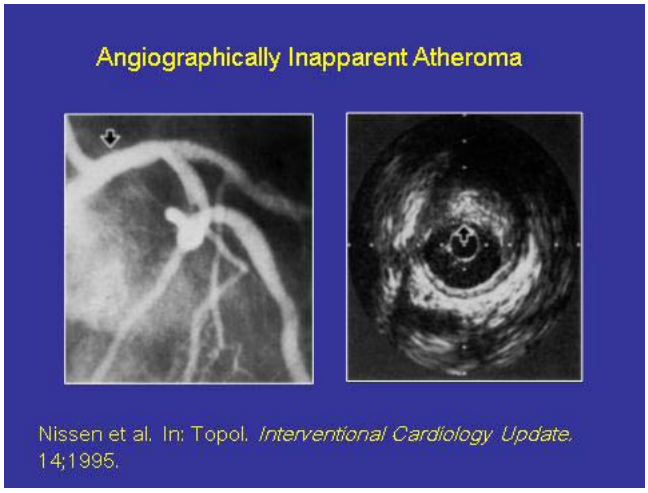

Figure 5: Coronary heart disease that is not detectable by angiogram (left) is clearly evident using computed tomography (right).

inflammation, oxidative stress, and immune dysfunction [6,13]. The data on saturated fats and endothelial dysvuntion and Cardiovascular disease remains controversial. [6,13]. 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 low-glycemic foods, monounsaturated fats, omega 3 fatty acids, polyphenols, and antioxidants can help to prevent post-prandial endothelial dysfunction [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 3) [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 4 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 with the subendothelium layer becoming thick but the lumen is still the same size. This extraluminal plaque and inflammation could be seen with electron beam tomography or Computed Tomography (CT) angiogram but missed by conventional coronary arteriogram (Figure 5). The image on the right in Figure 4 there is extensive extraluminal and intraluminal disease.

Lack of the proper type of imaging, ignoring the majority of the other 400 or so 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 and BP variability. Non dipping is defined as a less than 10% reduction in BP at night. Nocturnal BP is the primary determinate of CVD related to BP measurements. 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. 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 [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). Nocturnal blood pressure ismore clinically important than day blood pressure (27/15 mmHg difference is optimal) [8]. Furthermore, morning blood pressure surges (level and rapidity) increase the risk of ischemic stroke, MI, and left ventricular hypertrophy [8] Hypertension is not a disease, it is 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;
- Each increase of 20/10 mmHg doubles cardiovascular risk;
- Before age 50, the diastolic blood pressure predicts risk best;
- After age 50, the systolic blood pressure predicts risk best;
- 24-hour ambulatory blood pressure monitoring is more accurate than office 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: Percent over 140/90 mmHg should be less than 15 %.

Dyslipidemia is another one of the top 5 cardiovascular risk factor, but proper measurement using advanced lipid profiles is not often ordered to verify risk and optimal treatment (10,14, 15) An advanced lipid profile will measure:

- LDL-C total
- LDL-P 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 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) [8]. HDL-P (particle number) is most protective with larger HDL type 2b being a second important protective mechanism [10]. Larger number and size of HDL are more efficient at reverse cholesterol transport, and more protective to the vascular system in numerous other ways. It is also important to analyze dysfunctional HDL [10,14,15]. Patients who have a HDL of 85mg/dL or more often have dysfunctional HDL that is not even protective [14,15]. VLDL, triglycerides and remnant particles are very atherogenic and thrombogenic [10].

A s (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 is 140 mg, which again is currently classed as "normal,"CHD and MI are increased by 60%. Hyperinsulinemia is also an independent risk factor for CHD [2]. Insulin resistance creates inflammation, reduces nitric oxide levels, and causes endothelial dysfunction and vascular disease through the mitogen activated protein kinase (MAPK) pathway, which is atherogenic and induces hypertension 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 not just body weight, but BMI and body composition with visceral fat and lean body mass will help predict CHD risk [16].

Table 1: Non-invasive vascular testing for cardiovascular disease.

Endopat (endothelial dysfunction, Augmentation index and Heart rate variability)
CAPWA (computerized arterial pulse wave analysis)
HRV: Heart rate variability and HRRT(heart rate recovery time)
EKG
TMT (treadmill test)
MCG (magnetocardiography)
Structural Tests
Carotid IMT/Duplex
CT angiogram (CTA) with CAC (coronary artery calcium scoring)
Cardiac MRI (CMRI)
ECHO: Rest and exercise
ABI: (ankle brachial index): Rest and exercise
Retinal scan and OPA (Ocular Pulse Amplitude)
Cardiac PET, SPECT
FDG-PET/CT: vascular inflammation/plaque/biologic activity
PET/CT/F-NaF for coronary plaque/inflammation/morphology
PET/MRI for coronary plaque morphology and inflammation
IVUS: Intravascular ultrasound
Coronary angiogram

Fortunately, there are a number of non-invasive tests to determine vascular pathology before it actually starts [2]. A discussion of these techniques is beyond the scope of this paper; however I would urge the reader to find out more about these technologies, particularly EndoPAT, 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), Magnetic Cardiography (MCG) and Cardiac CT angiograms for calcium score [2,8,16-19] (Table 1). The ENDOPAT is the most cost effective and accurate noninvasive test the 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 and is very cost effective. Numerous other CHD risk factors are listed below in Table 2. Some of the most neglected and important CHD risk factors to evaluate include gender specific hormones, thyroid function, toxins, homocyteine and vitamin D. If proper coding is done, these and other tests reviewed are very cost effective and covered by insurance.

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 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. To do this we need to utilize new laboratory techniques, such as the advanced lipid profiles, 24 hour BP monitoring,

Table 2: Other Comprehensive Lab Testing for Cardiovascular Disease.

Advanced Lipid Testing
24 hour ABM
PRA and Aldosterone
Dysglycemia labs: adiponectin, FBS, 2hr GTT, insulin, proinsulin, C-peptide, A1C
BIA with regional fat and LMM
Markers for inflammation, oxidative stress and immune function
Micronutrient tests
Thrombosis markers
Renal function markers: CrCl, MAU, Cystatin C
Toxicology, heavy metals, POPs screen
Omega 3 index
Telomere test
CV Genetic SNP testing
CV Genetic Expression testing: Corus
Gluten testing
CBC with diff
UA
CMP 12
APO B and APO AI and AII
Free T4,T3, TSH, RT3, thyroid antibodies
Magnesium
Iron, TIBC and Ferritin
Fibrinogen
HSCRP and homocysteine
Uric acid
Microalbuminuria
GGTP and hepatic profile
Myeloperoxidase (MPO)
Plasma viscosity
Vitamin D 3
Hormone Profile: Free testosterone, SHBG, estradiol, estriol,progesterone, DHEA and DHEAS
EKG and TMT
Chest X Ray
CAPWA
ENDOPAT
ABI at rest and with exercise
APO E
ECHO
Carotid duplex and IMT
EBT and CT angio (CTA) with CAC score
Cardiac MRI
Retinal Scan
Mobile 0 Graph for central and brachial BP, AI, PWV.

and specific tests to identify inflammation such as HS-CRP, oxidative stress such as oxLDL and myeloperoxidase and immune vascular dysfunction. In addition vascular translational medicine will need to be evaluated with new imaging technologies, such as EndoPAT, CAPWA, carotid IMT m MCG 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. 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 damage.

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