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New Concepts in the Diagnosis and Non-Surgical Treatment of Cardiovascular 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. An understanding of the other 395 other CHD risk factors, as well as a more logical and in depth review of these top five risk factors are required. Within the top 5 CHD risk factors the items that should be included are 24 hour ambulatory blood pressure monitoring, advanced lipid profile testing, dysglycemic parameter measurements, visceral obesity evaluation with effects of adipokines and inclusion of lab tests to evaluate the three finite vascular endothelial responses including inflammation, oxidative stress and immune vascular dysfunction. An understanding of 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 re-evaluation as to diagnosis, prevention and integrative treatments. We have reached a limit in our ability to treat cardiovascular disease (CVD) appropriately [1]. Our present treatments are not effective in reducing vascular inflammation, oxidative stress and immune dysfunction which characterize the basic pathophysiology of vascular disease. CVD remains 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" [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 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 or they are not using appropriate techniques to identify and treat them. The concept of "vascular translational medicine" is important in this regard. For example, a patient may have several CHD biomarkers or risk factors and have normal endothelial function and arterial compliance or have no CHD biomarkers or risk factors and have extensive endothelial dysfunction, arterial stiffness and vascular disease. This gap in "translation of cause and effect" mandates a new approach to evaluation and treatment. What is important is the ability to diagnose vascular disease early and accurately utilizing a variety of non-invasive vascular tests for endothelial dysfunction, arterial compliance, pulse wave velocity (PWV), augmentation index (AI), carotid intimal medial thickness (IMT), carotid plaque, diastolic and systolic dysfunction and coronary calcium score. Thus, it is imperative that we now begin to examine other methods to detect early and aggressively prevent and treat CVD before clinical events occur [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. The ability to measure these finite responses allows early detection with aggressive management that addresses the initial vascular insult that results in the subclinical or clinical CVD. Treatment of these finite responses with proper nutrition, nutraceutical supplements, exercise, weight control, stress reduction integrated with optimal pharmacological therapies would allow for a more direct pathophysiological analysis and treatment that are cost effective in reducing CVD. For example, an elevated blood pressure may simply be a marker for a vascular dysfunction with endothelial dysfunction, loss of nitric oxide bioavailability, decrease

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arterial compliance that is secondary to one or all of these three finite responses. Treatment of the finite responses may reduce not only the blood pressure, but also improve the vascular dysfunction.

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, enter ocyte, the blood 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 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 75 mg/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 to preclinical 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 and metabolic memory

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 and ultimately CVD [2,4,8,9].

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 requires interruption. There are actually 38 different steps in this process that are important in the treatment of dyslipidemia- induced vascular disease [10].

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 the3 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 later can 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 that short-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

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 rennin-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 smooth muscle 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., 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 (PRR), toll-like receptors (TLR),

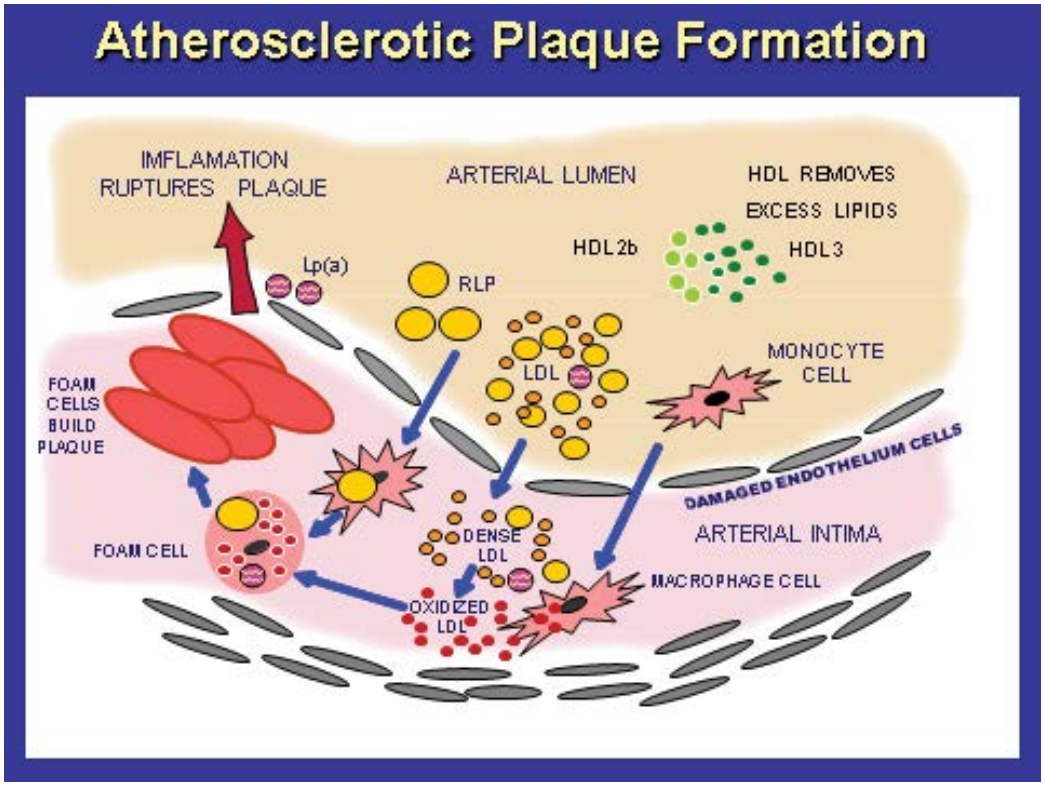

Figure 1: A simplified illustration of atherosclerotic plaque formation.

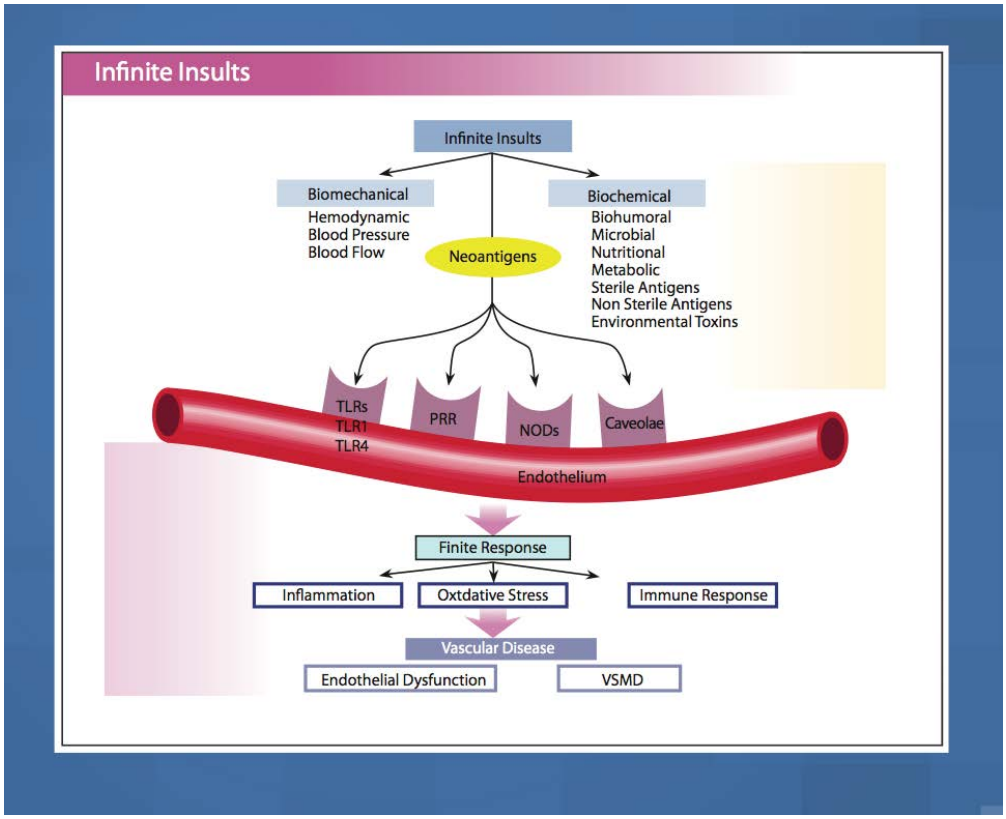

Figure 2: The endothelium is subject to an infinite number of insults but can only elicit a finite number of responses to those insults.

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 micro domains that when interrupted or stimulated reduce nitric oxide levels and increase 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 types of PRRs that are involved vascular membrane function and response to insults. There are many scientifically proven nutraceuticals and dietary factors that block the PRR (TLR and NLR) to reduce the downstream inflammation, oxidative stress and immune responses [12]:

- Curcurmin (tumeric): TLR 4, NOD 1 (NLR), and NOD 2 (NLR) (these are all PRR)
- Cinnamaldehyde (cinnamon): TLR 4
- Sulforaphane (broccoli): TLR 4
- Resveratrol (nutritional supplement, red wine, grapes): TLR 1
- Epigallocatechingallate (green tea) :TLR 1
- Luteolin (celery, green pepper, rosemary, carrots, oregano, oranges, olives: TLR 1
- Quercetin (tea, apples, onion, tomatoes, capers): TLR 1;
- Chrysin: 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, decrease immune vascular dysfunction, decrease CHD plaque formation, improve CHD and CHF symptoms and outcomes

The goalis touse a systematic (dynamic systems biology), functional and 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 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 foods containing saturated fats and trans fats, trigger gluco-toxicity, triglyceride toxicity, vascular endotoxemia, inflammation, oxidative stress, and immune dysfunction [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 and polyunsaturated fats, 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 sub-endothelium layer becoming thick but the lumen is still the same size. This extra luminal 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 extra-luminal and intraluminal disease.

Lack of the proper type of imaging, ignoring the majority of the other 395 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 hours between 3 AM 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 is more 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.

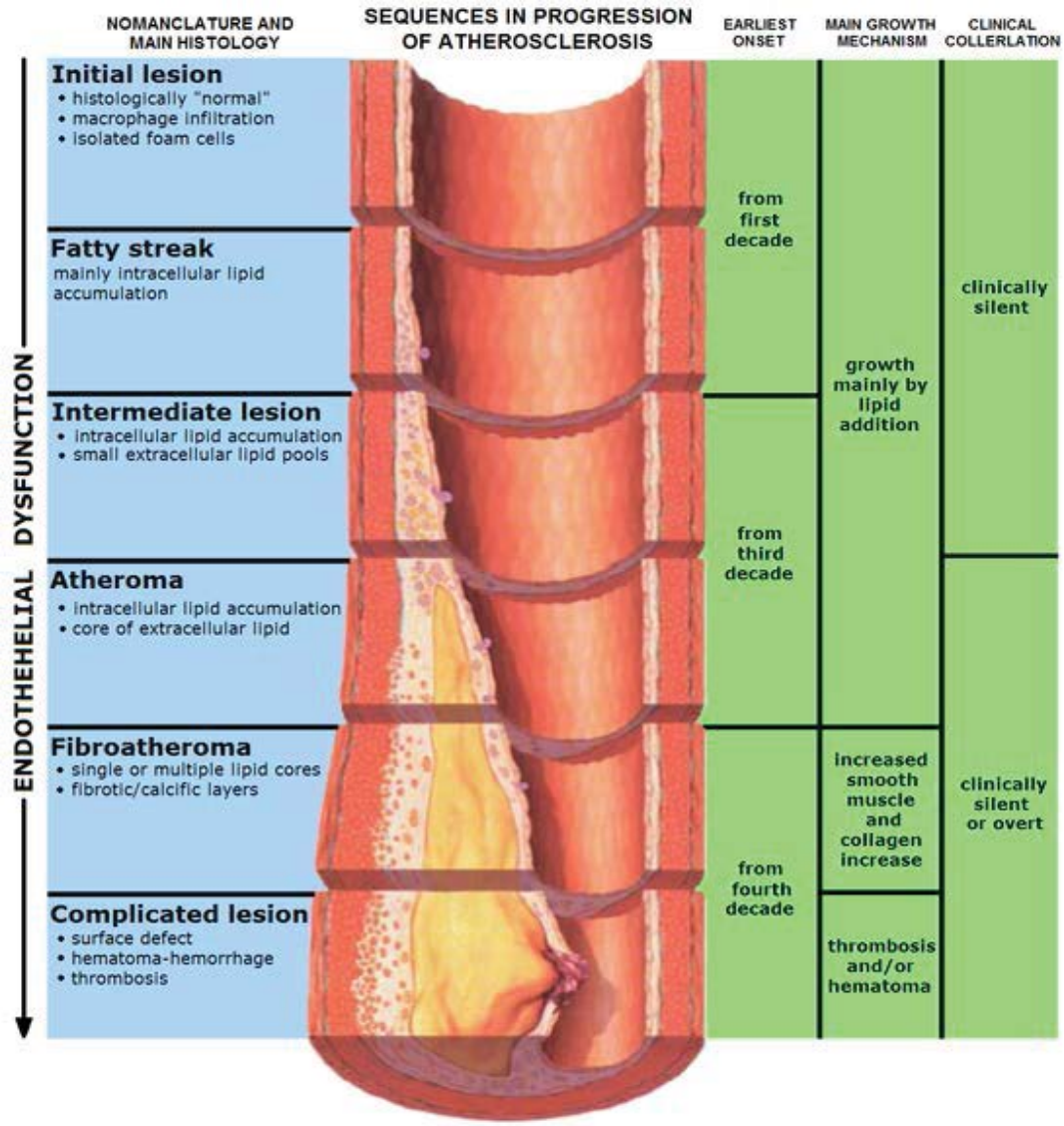

Figure 3: Progression of atherosclerosis.

- 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 (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
- Apo lipoprotein (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

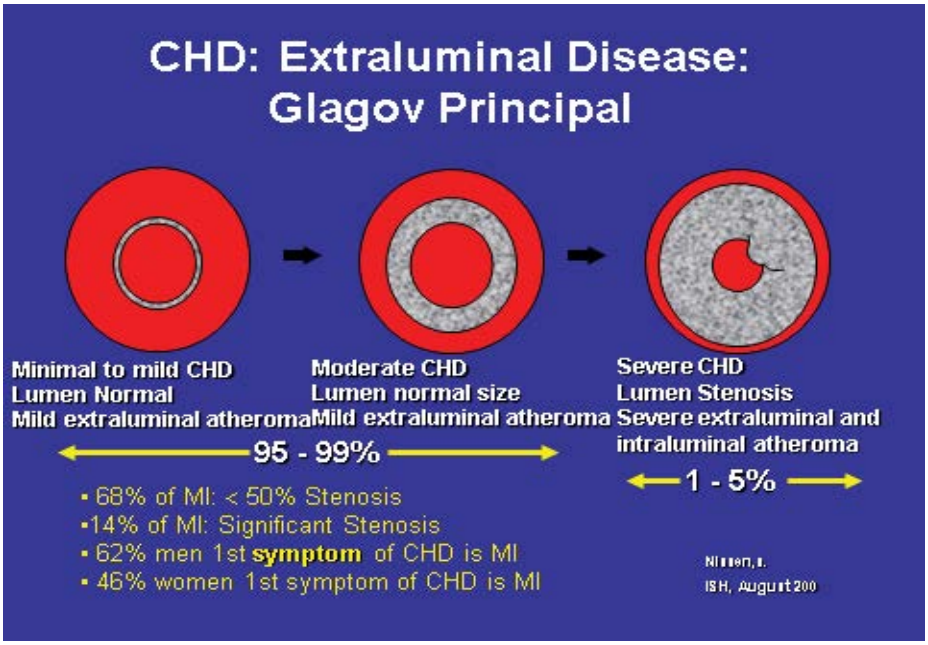

Figure 4: Illustration of the vessel changes that occur as coronary heart disease progresses.

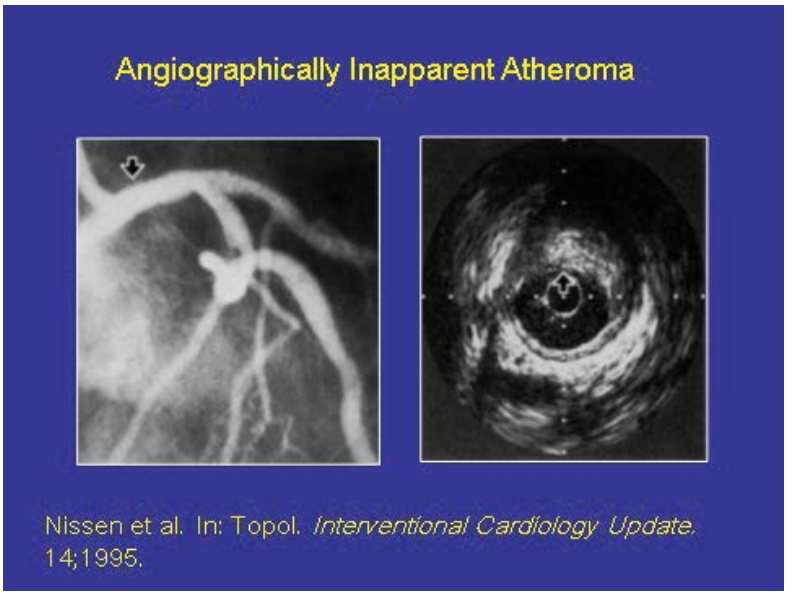

Figure 5: Coronary heart disease that is not detectable by angiogram (left) is clearly evident using computed tomography (right).

- Large VLDL
- VLDL-P particle number
- Remnant particles

The primary driving cardiovascular risk related to LDL-cholesterol is LDL-particle number (LDL-P) and Apo lipoprotein B particles [10]. 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 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/dL (often considered a normal level) the risk of CHD is increased by 25% [2]. A 2-hour glucose tolerance test (GTT) over 110 mg/dL increases CHD by 2% per 1 mg/dL increase in glucose [2]. The current definition of an abnormal 2-hour GTT is>140 mg/dL. If a patient's result is 140 mg/dL, 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, 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 as there may be a discrepancy between FBS and 2 hr GTT in many patients, or FBS may be normal but insulin levels are elevated which is an independent risk factor for CHD [16]. Also C-peptide may be abnormal long before the other glycation parameters

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]. Visceral fat is highly correlated with CHD, diabetes mellitus and metabolic syndrome and produces over 40 adipokines that can adversely affect CVD. Body weight and BMI are often misleading in properly evaluating body composition, body fat and lean muscle mass. Also, some patients who appear thin and are at their ideal body weight and BMI will have increased total fat by body composition analysis ("skinny fat") which increases their risk for CVD. Early and proper detection of body composition will direct treatment at an early stage and reduce CVD and future CVD-related health care costs.

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 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 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, homocysteine and vitamin D. Tests to evaluate the three finite responses are listed in Table 3. If proper coding is done, these and other tests reviewed are very cost effective and covered by insurance.

Conclusions

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, 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.

Functional Tests	Endopat: Endothelial Dysfunction
	CAPWA computerized arterial pulse wave analysis
	DTM digital thermographic monitor
	HRV: Heart Rate Variability
	EKG
	TMT
	MCG (magnetocardiography)
	OPA Ocular Pulse Amplitude
Structural Tests	Carotid IMT/Duplex
	EBT and CT Angiogram (CTA) with CAC scoring
	Cardiac MRI
	ECHO: Rest and exercise
	ABI: Rest and exercise
	Retinal Scan
Other	Cardiac PET and SPECT
	IVUS: Intravascular Ultrasound
	Cardiac Nuclear Studies (MPI) with PET and SPECT

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

Other Comprehensive Lab Test	CBC with diff and ESR
	UA
	CMP 12 with LDH and phosphorous
	Expanded advanced lipid profile
	APO B and APO AI and AII
	Free T4,T3, TSH, RT3, thyroid antibodies
	Magnesium
	Iron, TIBC and Ferritin
	Fibrinogen
	HSCRP
	Homocysteine
	Uric acid
	Microalbuminuria
	GGTP and hepatic profile
	Myeloperoxidase (MPO)
	Cardiovascular SNP's
	Toxicology and heavy metal screen : Spot or 24hr urine and blood
	24 hour urine VMA, CATS, METS, 17OH CS and KS, free cortisol and aldosterone
	Vitamin D 3
	Vitamin B 12 and folate
	Fasting C peptide, HBAIC, insulin, proinsulin, 2hr GTT
	PRA and Aldosterone
	Cortisol AM and PM and salivary cortisol as indicated
	Free testosterone, SHBG, estradiol, estriol. progesterone, DHEA and DHEAS
	EKG and TMT
	Heart Rate Variability
	Chest X Ray
	DEXA
	CAPWA
	ENDOPAT

Table 2: Other Comprehensive Lab Testing for Cardiovascular Disease.

Early and aggressive treatment can be started that will stop or slow the progression of CHD. Optimal nutrition (Mediterranean diet), aerobic and resistance exercise, ideal body weight and body composition, stress reduction, scientifically evaluated nutritional supplements(omega 3 fatty acids, Co Enzyme Q 10, curcumin, etc.) and integrated drug therapies should be able to prevent at least 80 percent of CVD. The reduction in health care costs would be enormous.

Finite Response Testing for Inflammation	HS-CRP
	MPO (myeloperoxidase)
	Interleukins IL-6 , IL 1b, TNF- alpha, IL-8, IL 10 and CAMs
	SAA (serum amyloid A)
	ESR
	Omega 3 Index
	Lp-PLA 2
	Fibrinogen and Ferritin
	NFkB
	PAI- I
	AGE's
	Homocysteine
	Waist circumference, visceral obesity % fat and total body fat
Finite Response testing for Oxidative Stress	Ox LDL and glycated LDL
	MPO
	GGT
	GSH and GSH/GSSG(reduced/oxidized ratio)
	MDA (Malondialdehyde) (JACC 2004;44:1996)
	TBARS (Thiobarbituric acid reactive substances) (JACC 2004;44:1996)
	F2 isoprostane and 8-OHdG(deoxyguanosine)
	Hexanoyl Lysine (ELISA) and lipid hydroperoxide: Lipids Ox
	Protein Carbonyl
	SOD 1 and 2 and Catalase
	Lp_PLA 2
	WBC with diff
	Uric acid
	Haptoglobin
	Oxidative Defense: TAS (total antioxidant status), Spectrox
Finite Response Testing for Immune Dysfunction	Thyroid antibodies
	ANA and RF (AHJ 2013;166:622)
	TGF b-1
	IL 1b, 4, 6,10,12, 17
	Interferon gamma
	IgG , IgE and IgA
	TNF alpha
	C4a, C3a, C3 and C4
	T lymphocyte subsets
	Total and epitope specific IgE and IgG-type 4
	NKC percent
	CBC with diff
	ELISA –ACT
	ACTH/Cortisol ratio
	MMP-9 and MMP-2
	VEGF
	Infectious disease profile with IGM and IGG antibodies such as H Pylori, CMV, EBV, Lyme, Mycoplasma, HSV, Chlamydia, Hepatitis A, B, C etc.

Table 3: Finite Response Testing for Inflammation, Oxidative Stress, Immune Dysfunction.

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. Proper and optimal evaluation and treatment of all of these CHD risk factors will hopefully decrease or halt subsequent vascular damage.

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