A Functional Approach to the Diagnosis and Treatment of Cardio-Metabolic Diseases

Joseph Lamb, MD
Applying Functional Medicine in Clinical Practice
Baltimore, Maryland
September 2011
Relevant Disclosures

JOSEPH LAMB, MD has indicated that he is an employee of the Functional Medicine Research Center at Metagenics, Inc. and of KinDex Therapeutics, Inc.
Objectives

• Identify physical findings and signs useful in a Functional Medicine assessment of the physiology and pathophysiology of cardiovascular diseases.
• Analyze diagnostic testing to effectively discriminate between normal and abnormal physiology specific to CVD and related endocrine disorders.
• Apply knowledge of lab testing to stratify risk and thus prioritize treatment focus based upon the individual patient.
• Select appropriate treatments for CVD and related endocrine disorders.
Decreased Mortality
Really?
“Are our patients really doing better?”
Rectangularizing the Survival Curve?

But **Have We Done It?**

“Empirical findings do not support recent compression of morbidity when morbidity is defined as major disease and mobility functioning loss.”

From 1998-2008,
- Length of life has increased; **yet**
- Prevalence of disease has increased, and
- Mobility and functioning have declined.

“I’m stuck in the middle.”
Patient outcomes will be unchanged if we do nothing!
Better Patient Outcomes
“Epigenetic changes represent a biological response to an environmental stressor. That response can be inherited through many generations via epigenetic marks...."
“So where am I going to find answers that my patients can use?”
An expanded understanding of physiology
**The Patient’s Story Retold**

<table>
<thead>
<tr>
<th>Antecedents  (Predisposing Factors- Genetic/Environmental)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triggering Events  (Activators)</td>
</tr>
<tr>
<td>Mediators/Perpetuators  (Contributors)</td>
</tr>
</tbody>
</table>

**Physiology and Function: Organizing the Patient’s Clinical Imbalances**

- **Assimilation** (e.g., Digestion, Absorption, Microbiota/GI, Respiration)
- **Defense & Repair** (e.g., Immune, Inflammation, Infection/Microbiota)
- **Structural Integrity** (e.g., from Subcellular Membranes to Musculoskeletal Structure)
- **Communication** (e.g., Endocrine, Neurotransmitters, Immune messengers)
- **Spiritual**
- **Transport** (e.g., Cardiovascular, Lymphatic System)

**Fundamental Lifestyle Factors**

<table>
<thead>
<tr>
<th>Sleep &amp; Relaxation</th>
<th>Exercise &amp; Movement</th>
<th>Nutrition &amp; Hydration</th>
<th>Stress &amp; Resilience</th>
<th>Relationships &amp; Networks</th>
</tr>
</thead>
</table>

**Name:** ______________________________  **Date:** ___________  **CC:** ______________________________

© Copyright 2011 Institute for Functional Medicine
Atherosclerosis
Lipid Hypothesis

Despite Virchow’s view on “irritation of vessel wall”, he proposed cholesterol as a prime etiologic agent in 1856.

Anitschkow demonstrated in rabbit feeding studies in 1913 the development of atherosclerosis with a high cholesterol diet.

Duff and McMillian mainstreamed this concept in 1951.

Atherosclerosis
Hypertension and Congestive Heart Failure
Metallo-Toxicity & Vascular Disease

“Heavy metal toxicity, especially mercury and cadmium, should be evaluated in any patient with hypertension, CHD, or other vascular disease.”


“The association between blood lead levels and increased all-cause and cardiovascular mortality was observed at substantially lower blood lead levels than previously reported.”

Oxidative Stress

“...hypertensive stimuli, such as high salt and angiotensin II, promote the production of ROS in the brain, the kidney, and the vasculature and that each of these sites contributes either to hypertension or to the untoward sequelae of this disease.”

Insulin Resistance
Clinical Consequences

Cognitive decline
Type 3 Diabetes
Sleep Apnea
PCOS
Malignancies
Erectile dysfunction
Gout
NAFLD
ESRD
Dyslipidemia
Hypertension
Atherosclerosis
Type 2 diabetes (5-7X)
Cardiovascular disease (2-4X)
Type 2 diabetes
CardioMetabolic Syndrome
Obesity
Sarcopenia
Dyslipidemia
Hypertension
Atherosclerosis
Malignancies
NAFLD
Acute ischemic stroke
Gout
Osteoporosis
ESRD
Metagenics
# Metabolic Syndrome and Body Composition

<table>
<thead>
<tr>
<th>BMI</th>
<th>% Body Fat Male/Female</th>
<th>Prevalence of Metabolic Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.5–24.9</td>
<td>12 / 24</td>
<td>4.8%</td>
</tr>
<tr>
<td>25–29.9</td>
<td>21 / 31</td>
<td>22.8%</td>
</tr>
<tr>
<td>30–34.9</td>
<td>29 / 37</td>
<td>60.2%</td>
</tr>
<tr>
<td>&gt; 35</td>
<td>36 / 43</td>
<td>&gt; 90 %</td>
</tr>
</tbody>
</table>

Persistent Organic Pollutants

“BMI was associated with prevalent diabetes only among persons with high normal serum GGT activity (p=0.002).”

Arsenic and Diabetes

“Elevated mortality rates were observed for both males and females for all diseases of the circulatory system [SMR ≈ 1.13], cerebrovascular diseases [SMR = 1.19], diabetes mellitus [SMR ≈ 1.28], and kidney diseases [SMR ≈ 1.33].

Preadipocyte Maturation

Cell Biology:
- Dexamethasone
- Insulin
- 3-isobutyl-1-methylxanthine

Real Life:
- Monday morning stress
- 60 MPH commuting
- Highly sugared 4 shot latte

3T3-L1 Preadipocytes
Intestinal Hyperpermeability
High Fat Diet and Endotoxemia

“Baseline endotoxin concentrations were 8.2 pg/mL but increased significantly (P < 0.05) by approximately 50% after a high-fat meal.”

Insulin Resistance and Endotoxemia

“Endotoxemia induced systemic insulin resistance as demonstrated by a 35% decrease in insulin sensitivity (p<0.005) while there was no effect on pancreatic beta-cell function.”

“We demonstrate, for the first time in humans, that acute inflammation induces systemic IR following modulation of specific adipose inflammatory and insulin signaling pathways.”

Endothelial Dysfunction
Endothelial Dysfunction

- Hyperglycemia, oxLDL, dysfxn HDL
- Inhibition of monocyte adhesion
- Platelet inhibition
- AKT
- PKCβ2
- eNOS
- NO + L-citrulline
- Guanylyl cyclase
  - GTP → cGMP
- Endothelial cells
- Smooth muscle cell relaxation and growth inhibition
- Lumen
- Shear stress, HDL
- O2 + L-arginine
  - Ca2+, FAD
  - NADPH, TH4

Shared Mechanisms

“The most important stimulus for the continuous production of NO is viscous drag related to blood flow across the endothelium.”

Dimmeler S et al. 1999.
PKC$\beta_{II}$ Inhibition

Ruboxistaurin (RBX) – a PKC$\beta_{II}$ inhibitor

- Normalizes eNOS activity in rat glomerular endothelial cells that is decreased in response to glucose-induced PKC$\beta$ activation
- In a multi-center, double blind RCT, 123 subjects with Type II DM and proteinuria received 32 mg RBX or placebo
  - RBX significantly decreased albuminuria by 24% compared with 9% by placebo
  - RBX maintained renal function after 1 year while placebo subjects experienced a significant loss

Flow Mediated Vasodilation

Shimokawa, 2000. 64th Annual Society Meeting of the Japanese Circulation Society.
FMD and Cholesterol

CARE Study
Pravastatin
Simvastatin

FMD: Prognostic Tool

Modena et al measured brachial artery FMD after 6 months treatment for HTN in 400 postmenopausal women followed for 4 years.

CVE rate 6.0% (0.5/100 patient years) with improved FMD.

CVE rate 21.3% (3.5/100 patient years) with persistently impaired FMD.

Modena MG et al. JACC 2002.
Nitric Oxide Physiology
Nitrate-Nitrite-NO Cycle

Nitrite is a Signaling Molecule

“We further find that nitrite readily affects cyclic GMP production, cytochrome P450 activities, and heat shock protein 70 and heme oxygenase-1 expression in a variety of tissues. These cellular activities of nitrite, combined with its stability and abundance in vivo, suggest that this anion has a distinct and important signaling role in mammalian biology, perhaps by serving as an endocrine messenger and synchronizing agent.”

Myocardial Reperfusion Injury

“Mice fed a standard diet with supplementation of nitrite (50 mg/liter) in their drinking water for 7 days exhibited significantly higher plasma levels of nitrite, ... and displayed a 48% reduction in infarct size after MI/R.

Arginine Therapy in Acute MI

“L-arginine (3 grams tid), when added to standard postinfarction therapies, does not improve vascular stiffness measurements or ejection fraction and may be associated with higher postinfarction mortality. L-arginine should not be recommended following acute myocardial infarction.”

Physiological Effects of Dietary Nitrite

“Mice fed a cholesterol-enriched diet exhibited significantly elevated leukocyte adhesion to and emigration through the venular endothelium as well as impaired endothelium-dependent relaxation in arterioles. Administration of nitrite in the drinking water inhibited the leukocyte adhesion and emigration and prevented the arteriolar dysfunction.

Nitrite/Nitric Oxide Pool

“These observations hint at conserved roles for the Nitrite-NO pool in cellular processes such as oxygen-sensing and oxygen-dependent modulation of intermediary metabolism.”

Obesity: Energy Partitioning
“TLRs are present in adipocytes and can be directly activated by nutrients, particularly fatty acids.”

ER Stress

Excess nutrient intake is a major contributor to obesity. Research implicates endoplasmic reticulum stress as an early consequence of nutrient excess and cause for IR and inflammation.

Diagnosis: From Pathophysiology to Intervention
Lab Testing

Performance
- Accuracy
- Precision
- Sensitivity and Specificity
- Predictive Power
- Baye’s Theorem

<table>
<thead>
<tr>
<th></th>
<th>Abnormal test result</th>
<th>Normal test result</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease Absent</td>
<td>A</td>
<td>B</td>
<td>A+B</td>
</tr>
<tr>
<td>Disease Present</td>
<td>C</td>
<td>D</td>
<td>C+D</td>
</tr>
<tr>
<td>Total</td>
<td>A+C</td>
<td>B+D</td>
<td>A+B+C+D</td>
</tr>
</tbody>
</table>

**Sensitivity** \((C/C+D)\): fraction of all those with the disease who get a **positive** result

**Specificity** \((B/B+A)\): fraction of all those **without the disease** who get a **negative** results

**Positive Predictive value** \((C/A+C)\): fraction of all **positive results** who have the disease (true positives)

**Negative Predictive value** \((B/B+D)\): fraction of all **negative results** who don’t have the disease (true negatives)

Diagnosis: Hyperlipidemia and Atherosclerosis
<table>
<thead>
<tr>
<th>Analyte</th>
<th>Optimal</th>
<th>Desirable</th>
<th>Threshold for Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>≤ 150</td>
<td>≤ 200</td>
<td>≥ 200</td>
</tr>
<tr>
<td>HDL (female)</td>
<td></td>
<td>≥ 50</td>
<td>≤ 50</td>
</tr>
<tr>
<td>HDL (male)</td>
<td></td>
<td>≥ 40</td>
<td>≤ 40</td>
</tr>
<tr>
<td>TG</td>
<td>≤ 100</td>
<td>≤ 150</td>
<td>≥ 150</td>
</tr>
<tr>
<td>TG/HDL</td>
<td>≤ 3</td>
<td>≤ 4</td>
<td>≥ 4</td>
</tr>
<tr>
<td>LDL</td>
<td>≤ 100</td>
<td>≤ 130</td>
<td>≥ 160</td>
</tr>
</tbody>
</table>

Units are mg/dl
Apo B/Apo A-1 ratio

“The apo B/apo A-1 ratio could be a simple, robust, precise indicator of great value in health screening and during lipid-lowering therapy.”

“A ratio of apo B/apo A-1 of 0.7 or lower would be considered lower risk, whereas a ratio of 0.8 or higher would represent an elevated risk.”

ApoB Superior to LDL

“Error is not avoided because it is ignored. Thus, the almost universal practice of measuring one sample unquestionably makes care simpler, but with the consequence that important decisions are inevitably based on less than acceptably accurate information. This is especially true for LDL-C measurement.”

### Oxidized LDL - Predictive Biomarker for CVD

Unadjusted odds ratios and 95% confidence intervals for coronary artery disease for various lipid and lipoprotein biomarkers.

An odds ratio of 1 implies that the event is *equally likely* in both groups.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>1.20 (0.93-1.56)</td>
</tr>
<tr>
<td>LDL</td>
<td>1.90 (1.44-2.51)</td>
</tr>
<tr>
<td>Lp-PLA2&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2.02 (1.54-2.66)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>2.34 (1.79-3.05)</td>
</tr>
<tr>
<td>Total cholesterol/HDL</td>
<td>6.12 (4.56-8.20)</td>
</tr>
<tr>
<td>1/HDL</td>
<td>6.61 (4.93-8.86)</td>
</tr>
<tr>
<td><strong>Oxidized LDL</strong></td>
<td><strong>8.26 (6.15-11.11)</strong></td>
</tr>
<tr>
<td><strong>Oxidized LDL/HDL</strong></td>
<td><strong>13.92 (10.07-19.23)</strong></td>
</tr>
</tbody>
</table>

<sup>1</sup> Lipoprotein-associated phospholipase A2

*Johnston et al* Am J Cardiol 2006;97:640–645
Electron Beam Computed Tomography
## Calcium Score and Cardiac Risk

<table>
<thead>
<tr>
<th>Calcium Score</th>
<th>Probability of CAD (&gt; 80% stenosis)</th>
<th>Cardiac Risk Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low &lt; 5%</td>
<td>Minimal</td>
</tr>
<tr>
<td>1-10</td>
<td>Low &lt; 10%</td>
<td>Low</td>
</tr>
<tr>
<td>11-100</td>
<td>Mild Stenosis</td>
<td>Moderate</td>
</tr>
<tr>
<td>101-400</td>
<td>Nonobstructive disease, may have stenosis</td>
<td>Likely</td>
</tr>
<tr>
<td>&gt; 400</td>
<td>High likelihood (&gt; 90%) of at least one stenosis</td>
<td>High</td>
</tr>
</tbody>
</table>

Carotid Intima-Medial Thickness

Figure 2. Carotid IMT measurement.

Source: G.B.J. Mancini.

“In this community-based cohort of patients with ACS, Lp-PLA2 was strongly and independently associated with major adverse cardiac events and contributed incrementally to risk discrimination.”

hs-CRP and CAD

“Rosuvastatin lowered CRP (37%), LDL (50%), nonfatal myocardial infarction (55%), nonfatal stroke (48%), hospitalization and revascularization (47%), and all-cause mortality (20%).”

“Approximately 4.3% of the population satisfies Jupiter inclusion criteria.”

## Risk Assessment

<table>
<thead>
<tr>
<th>Framingham Risk Score</th>
<th>Reynolds Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>Blood Pressure</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Smoking</td>
<td>Smoking</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>Total cholesterol</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>HDL cholesterol</td>
</tr>
<tr>
<td></td>
<td><strong>hs-CRP</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Parental history of MI</strong></td>
</tr>
</tbody>
</table>

KIF6

A single nucleotide polymorphism (SNP) in KIF6, a member of the KIF9 family of kinesins, is associated with differential coronary event reduction from statin therapy in four randomized controlled trials; this SNP (rs20455) is also associated with the risk for coronary heart disease (CHD) in multiple prospective studies. These analyses revealed that two SNPs (rs9462535 and rs9471077), in addition to rs20455, were associated with event reduction from statin therapy (P (interaction) < 0.1 in each of the three studies). The relative risk reduction ranged from 37 to 50% (P < 0.01) in carriers of the minor alleles of these SNPs and from -4 to 13% (P > 0.4) in non-carriers.

Clinical Biomarkers

- **Apo B**
  - Male: 52-109 mg/dl
  - Female: 49-103 mg/dl
- **ApoB/Apo A1 Ratio**
  - < 0.6
- **Lp-associated PLA2**
  - < 300 ng/ml
- **hs-CRP**
  - < 0.6 mg/L
- **KIF6**
  - + SNPs
- **Lipoprotein (a)**
  - < 30 mg/dl
- **Homocysteine**
  - < 7 mmol/L
- **Uric acid**
  - < 5.0 mg/dl
Diagnosis: Hypertension
What is Hypertension?

<table>
<thead>
<tr>
<th>Category</th>
<th>JNC 6</th>
<th>JNC 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>≤ 130/90</td>
<td>≤ 110/70</td>
</tr>
<tr>
<td>Normal</td>
<td>≤ 130/90</td>
<td>≤ 120/80</td>
</tr>
<tr>
<td>Borderline/Pre</td>
<td>130-140/90-95</td>
<td>120-139/80-89</td>
</tr>
<tr>
<td>Hypertensive 1</td>
<td>140/95</td>
<td>140-159/90-99</td>
</tr>
<tr>
<td>Hypertension 2</td>
<td></td>
<td>≥ 160/100</td>
</tr>
</tbody>
</table>
Important JNC 7 Take-homes

- In those older than age 50, systolic BP of greater than 140 mm Hg is a more important CVD risk factor than diastolic BP.
- Beginning at 115/75 mm Hg, CVD risk doubles for each increment of 20/10 mm Hg.
- Those who are normotensive at 55 years of age will have a 90% lifetime risk of developing hypertension.
- Prehypertensive individuals require health-promoting lifestyle modifications to prevent the progressive rise in blood pressure and CVD.

White Coat Hypertension
Diagnosis: Dysinsulinemia
What is CardioMetabolic Syndrome?

Abdominal obesity

Pro-inflammatory state

Insulin resistance

Pro-thrombotic state

Atherogenic dyslipidemia

Elevated blood pressure

# Components of Metabolic Syndrome

**AHA/NHLBI Scientific Statement**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Categorical Cut Points</th>
</tr>
</thead>
</table>
| Elevated Waist Circumference   | ≥ 40 inches in men  
|                                | ≥ 35 inches in women                                       |
| Elevated TG                    | ≥ 150 mg/dL (or drug tx for elevated TG)                    |
| Reduced HDL-C                  | < 40 mg/dL in men  
|                                | < 50 mg/dL in women                                       |
| Elevated BP                    | ≥ 130 mm Hg systolic BP or ≥ 85 mm Hg diastolic BP or drug tx for HTN |
| Elevated fasting glucose       | ≥ 100 mg/dL or drug tx for elevated glucose                |

What is Diabetes?

Insulin deficiency or something more??
A Simple Test for Insulin Resistance

TG/HDL Ratio

≤ 3.0  normal

≈ 5.0  suggestive of insulin resistance

≥ 8.0  diagnostic of insulin resistance

Hemoglobin A1c

Maintenance

< 6.0  normal
6.0 - < 7.0  good control
7.0 - < 8.0  fair control
≥ 8.0  poor control

Diagnostic

< 5.5  normal
≥ 5.5  insulin resistance
≥ 6.5  diabetes mellitus

Louis Camille Maillard (1878-1936)
2-hour Glucose Tolerance Test

Symptoms of diabetes plus random blood glucose concentration ≥ 200 mg/dl
or
Fasting glucose ≥ 125 mg/dl
or
Two hour glucose ≥ 200 mg/dl during an oral glucose tolerance test

(In the absence of unequivocal hyperglycemia and acute metabolic decompensation, confirmation by repeat testing on a different day is recommended.)

Continuum of Insulin Resistance

Microalbuminuria and Risk of CHD

N=2,085; 10-year follow-up

## Definition of Microalbuminuria and Macroalbuminuria

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Microalbuminuria</th>
<th>Macroalbuminuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine AER (µg/min)</td>
<td>&lt;20</td>
<td>20-200</td>
<td>&gt;200</td>
</tr>
<tr>
<td>Urine AER (mg/24h)</td>
<td>&lt;30</td>
<td>30-300</td>
<td>&gt;300</td>
</tr>
<tr>
<td>Urine Albumin/Cr ratio (mg/gm)</td>
<td>&lt;30</td>
<td>30-300</td>
<td>&gt;300</td>
</tr>
</tbody>
</table>
Microalbuminuria

UAE < 30 mg/day (below the conventionally used limit):

- is associated with an adverse CV risk
- is sensitive to interventions that reduce obesity, BP, and IR

Interventions
Healthy Lifestyles – an Uphill Journey
Lifestyle Superior to Metformin

- N=3234 nondiabetic persons with elevated glucose assigned to either placebo, metformin (850 mg bid), lifestyle modification.
- Lifestyle intervention reduced incidence of diabetes by 58% and metformin by 31% as compared with placebo.

Diabetes Prevention Program Research Group

NEJM 2002;346(6): 393-403.
Accepted Therapy

The NCEP-ATPIII guidelines recommend 12 weeks of “therapeutic lifestyle change” as “first line treatment for hypercholesterolemia.”
What Are We Missing?

Trouble with Healthy Lifestyle?

% of Americans who have tried to lose weight; ’90,’99 & ‘05

Gallup poll that asked Americans, “How many different times, if any, have you tried to lose weight?”

The number of weight loss attempts is steadily increasing

<table>
<thead>
<tr>
<th>Frequency</th>
<th>1990</th>
<th>1999</th>
<th>2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least Once</td>
<td>56%</td>
<td>66%</td>
<td></td>
</tr>
<tr>
<td>Once or Twice</td>
<td>30%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>3 to 10 times</td>
<td>18%</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>More than 10</td>
<td>5%</td>
<td>11%</td>
<td></td>
</tr>
</tbody>
</table>

The Gallup Organization
Our genes haven’t changed, but our environment has...

“It is theorized that the metabolic syndrome may be a manifestation of the profound mismatch between our present environment and previous circumstances that have molded evolutionary selection.”

Lifestyle Intervention

Support for Dietary Change
Review of Dietary Therapy for Type 2 DM

36 articles reporting a total of 18 trials following 1467 participants were included:

- Low-fat/high-carbohydrate diets
- High-fat/low-carbohydrate diets
- Low-calorie (1000 kcal per day)
- Very-low-calorie (500 kcal per day) diets
- Modified fat diets
- American Diabetes Association exchange diet

“There are no high quality data on the efficacy of the dietary treatment of type 2 diabetes...”

Gene-Nutrient Interactions

“Healthy living habits (including healthy diet and regular exercise) and gene-activating xenobiotics upregulate mechanisms that produce lipoprotein patterns typical of very old people and enhance longevity.”

Enhanced Understanding

“Complementary study of food and food patterns and of nutrients and specific food constituents will enhance the understanding of diet and health.”

Jacobs et al. AJCN 2003;78:508-513S.
The Mediterranean Diet

“A dietary pattern that includes cereals, fish, legumes, vegetables, and fruits was independently associated with reduced levels of clinical and biological markers linked to the metabolic syndrome, whereas meat and alcohol intake showed the opposite results.”

The HALE Study

“Among individuals aged 70 to 90 years, adherence to a Mediterranean diet and healthful lifestyle is associated with more than a 50% lower rate of all-causes and cause-specific mortality.”

Low-Glycemic Load Med Diet

“Only the low carbohydrate Mediterranean diet improved HDL Levels and was superior to both the ADA and traditional Mediterranean diet in improving glycemic control.”

the FUNGENUT Study

“We detected 71 down-regulated genes in the rye-pasta group, including genes linked to insulin signaling and apoptosis.

In contrast, the...oat-wheat-potato diet up-regulated 62 genes related to stress, cytokine-chemokine-mediated immunity, and the interleukin pathway.”

“The relatively recent focus on nutrients parallels an increasing discrepancy between theory and practice: the greater the focus on nutrients; the less healthful foods have been become.”

Lifestyle Intervention

Support for Other Changes
Benefit of Exercise

• “With each additional healthy lifestyle factor, cardiometabolic risk decreased by 31 %.”
• “A higher healthy lifestyle score was associated with a lower prevalence of cardiometabolic risk .”
• “Compared with individuals having 0-1 healthy lifestyle behaviours, those with 5 or 6 healthy lifestyle behaviours had a 70 % lower prevalence of cardiometabolic risk.”

“The healthy lifestyle factors included fruit and vegetable intake ≥ 5 servings/d, meat intake ≤ 2 servings/d, never smoking, consuming 2-6 alcoholic drinks/week, television viewing time ≤ 2 h/d and moderate to vigorous physical activity ≥ 4 h/week.”

Exercise

- In 6 year follow-up, 1970 individuals (25%) developed MetSyn.
- The odds ratios of incident MetSyn was 0.80 for subjects in the highest quartile of leisure-time physical activity.

Sleep and Circadian Rhythms

“… disorders of circadian behavior and sleep are associated with increased hunger, decreased glucose and lipid metabolism, and broad changes in the hormonal signals involved in satiety.”


“The amount of human sleep contributes to the maintenance of fat-free body mass at times of decreased energy intake.”

Cognitive Behavioral Therapy

During a mean 94 months of follow-up, the intervention group had a 41% lower rate of fatal and nonfatal first recurrent CVD events (hazard ratio [95% confidence interval], 0.59 [0.42-0.83]; P = .002), 45% fewer recurrent acute myocardial infarctions (0.55 [0.36-0.85]; P = .007), and a nonsignificant 28% lower all-cause mortality (0.72 [0.40-1.30]; P = .28) than the reference group after adjustment for other outcome-affecting variables. In the CBT group there was a strong dose-response effect between intervention group attendance and outcome.

Clinical Questions and Solutions
“What do you do for high LDL and low HDL?”
Beyond Statins

“In patients with familial hypercholesterolemia, combined therapy with ezetimibe and simvastatin did not result in a significant difference in changes in intima-media thickness, as compared with simvastatin alone, despite decreases in LDL levels.”

Niacin Superior to Ezetimibe

“This comparative effectiveness trial shows that the use of extended-release niacin causes a significant regression of carotid intima-media thickness.” The patients involved in this study had a starting LDL that was <100 mg/dl and an average baseline hsCRP of 1.6 mg/dl.

Effects of Niacin on cIMT

“Post-hoc subgroup analysis revealed an improvement in FMD in patients with low HDL-C at baseline (P=0.047). The present findings indicate that ER-niacin treatment improves endothelial dysfunction in patients with CAD and low HDL-C, but not with normal HDL-C.”


Effects of Niacin on FMD
Pleiotropic Effects

“Niacin (2 g daily) raises HDL, lowers LDL, Triglycerides, and Lp(a) Lipoprotein levels by about 15%. Because of the pleiotropic effects of niacin, this study demonstrates that its effects on increasing HDL levels are more important than lowering LDL levels in regression of carotid intima-media thickness.”

Blumenthal R et al. NEJM 2009; 361-63.
“These findings indicate for the first time that niacin inhibits vascular inflammation by decreasing endothelial ROS production and subsequent LDL oxidation and inflammatory cytokine production, key events involved in atherogenesis.”

AIM-HIGH

• 3500 subjects – 90 sites – 32 month
• Favorable changes in HDL and TG
• Small unexplained increase risk for ischemic stroke (28 v. 12)

Caveats:
• Excellent LDL control
• Other High Risk Groups (HDL - known risk factor)
• Intent to Treat Data Set (9 discontinued)
• Postmarketing Experience: 6M patient years
• Inconsistent mechanisms
HDL Functionality

“Concentrations of HDL-C were inversely related to CHD events. Multivariable Cox proportional hazards analysis showed that CHD events were reduced by 11% with gemfibrozil for every 5-mg/dL (0.13-mmol/L) increase in HDL-C (P = .02).”


“Upon LPS administration, profound changes in 21 markers were observed in the proteome in both study groups. Hierarchical clustering ...revealed 3 distinct clusters, which were largely independent of baseline HDL cholesterol levels but correlated with paraoxonase 1 activity.

# Niacin Recommendations

<table>
<thead>
<tr>
<th>Indications</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemia</td>
<td>ER Niacin 500mg 1-2 tablets twice daily</td>
</tr>
<tr>
<td>Endothelial Dysfunction Abnormal cIMT</td>
<td>ER Niacin 500mg 1-2 tablets twice daily</td>
</tr>
</tbody>
</table>

**Cautions:**
- Monitor LFTs. Hepatotoxicity increased at doses ≥ 2000 mgs.
- Adjust dosing with history chromium use, arginine use and prior hx gout.
- May consider initial use ASA 325 mg daily.
“Oxidative Stress...?”
Electron Transport Chain

http://www.biochem.oulu.fi/proteomics/ymp_comparison.html
Depletion of CoQ10 by Statins

“A dose-related significant decline of the total serum level of coenzyme Q10 was found in the pravastatin group from 1.27 +/- 0.34 at baseline to 1.02 +/- 0.31 mmol/l at the end of the study period (mean +/- S.D.), P < 0.01. After lovastatin therapy the decrease was significant as well and more pronounced, from 1.18 +/- 0.36 to 0.84 +/- 0.17 mmol/l, P < 0.001.”

Synthesis of Co-Q10
Statin-Induced Myalgias

Muscle structure was essentially normal in 14 patients and showed evidence of mitochondrial dysfunction and nonspecific myopathic changes in 2 patients each. Muscle CoQ10 concentration was not statistically different between patients and control subjects, but it was more than 2 SDs below the normal mean in 3 patients and more than 1 SD below normal in 7 patients.

CoQ10 Improves Endothelial Function

CoQ(10) supplementation improved endothelial dysfunction in statin-treated type 2 diabetic patients, possibly by altering local vascular oxidative stress.

# CoQ10 Recommendations

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin Use</td>
<td>100 mg daily</td>
</tr>
<tr>
<td>Hx Statin-associated Myopathy</td>
<td>≥ 200 mg daily</td>
</tr>
<tr>
<td>Hypertension</td>
<td>100 – 225 mg daily (initial 200 mg/d)</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>150 – 400 mg daily (favor higher end)</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>200 – 600 mg daily (initial 400 mg/d)</td>
</tr>
<tr>
<td>Chronic Stable Angina</td>
<td>150 – 200 mg daily</td>
</tr>
<tr>
<td>Post MI</td>
<td>100 – 120 mg daily</td>
</tr>
<tr>
<td>Endurance Athletes</td>
<td>≥ 300 mg daily (?)</td>
</tr>
</tbody>
</table>
“I am concerned about calcium and the risk for Heart Disease.”
“Calcium Supplements (without coadministered vitamin D) are associated with an increased risk of myocardial infarction.”


“Evidence from limited data suggests that ... calcium supplements seem to have minimal cardiovascular effects.”

Vitamin D and CV Risk

“Low serum levels of 25(OH)D are associated with increased cardiovascular mortality in a nationally representative US sample.”

Fiscella K et al. Ann Fam Med 2010.

“Evidence from limited data suggests that vitamin D supplements at moderate to high dose may reduce CV risk....”

“Vitamin D deficiency is common in patients with Type 2 diabetes during winter in Scotland. A single large dose of Vitamin D improves endothelial function in patients with Type 2 Diabetes and vitamin D insufficiency.”

# Vitamin D Recommendations

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficiency States (&lt; 25 ng/ml)</td>
<td>10,000 units D3 daily</td>
</tr>
<tr>
<td>Maintenance (&gt; 30 ng/ml) (Goal 40-60 ng/ml)</td>
<td>5,000 units D3 daily</td>
</tr>
<tr>
<td>Autoimmune Disease (Goal 60-80 ng/ml)</td>
<td>10,000 units D3 daily</td>
</tr>
</tbody>
</table>

**Cautions:**
- Monitor both 25(OH) Vitamin D3 and 1,25 di(OH) Vitamin D3 levels.
- Endogenous synthesis after sunbathing ≈ 10,000 units/day.
“Are you still treating hyperhomocysteinemia?”
## Primary Prevention

### TABLE 2

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Age Range (Yrs)</th>
<th>Women (%)</th>
<th>Variable of Interest</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cui et al (2010)</td>
<td>58,730</td>
<td>40–79</td>
<td>61</td>
<td>Intake of folate, B₆, and B₁₂</td>
<td>Inverse association between dietary folate and vitamin B₆ and death from cardiovascular disease (multiple end points)</td>
</tr>
<tr>
<td>Liu et al (1999)</td>
<td>75,521</td>
<td>38–63</td>
<td>100</td>
<td>Intake of whole grains</td>
<td>Up to 33% lower rate of fatal myocardial infarction (MI), coronary heart disease (CHD), and nonfatal MI (P &lt; .001)</td>
</tr>
<tr>
<td>Liu et al (2000)</td>
<td>75,521</td>
<td>38–63</td>
<td>100</td>
<td>Intake of whole grains</td>
<td>Up to 51% lower rate of ischemic strokes (P = .003)</td>
</tr>
<tr>
<td>Merchant et al (2003)</td>
<td>46,036</td>
<td>40–75</td>
<td>0</td>
<td>B-vitamin intake</td>
<td>21% lower rate of peripheral arterial disease for every 400 μmol/L increase in intake (95% CI 0.64–0.96)</td>
</tr>
<tr>
<td>Rimm et al (1998)</td>
<td>80,082</td>
<td>30–55</td>
<td>100</td>
<td>Intake of folic acid and vitamin B₆</td>
<td>31% lower rate of nonfatal MI and fatal CHD (95% CI 0.55–0.87)</td>
</tr>
</tbody>
</table>

“Daily administration of folic acid, vitamin B6, and vitamin B12 to patients with recent stroke or transient ischaemic attack was safe but did not seem to be more effective than placebo in reducing the incidence of major vascular events.”


“Long-term treatment of poststroke survivors with folic acid, B6, and B12 was associated with a reduction in the hazard of major depression in our patient population.”

Beyond Homocysteine - Methylation

DNA Methylation

- BH₂
- BH₃
- Coupling of NOS
- Antioxidant
- ATP

Endothelial function → Cardioprotection

The Internet Journal of Anesthesiology™
5-MTHF or Folic Acid

“5-MTHF has beneficial results on endothelial dysfunction and vascular superoxide production in human atherosclerosis....”


“... the frequency of micronucleated binucleate cells was significantly lower at 120 nM folic acid compared with 120 nM 5-MTHF.”

Further Mechanisms

1. N-homocysteinylation alters function of proteins (including metallothioneins) by addition of free thiol groups and inactivation of free amino groups altering redox potential.

2. Modified proteins can act as neoantigens and initiate the inflammatory response.

3. HDL particles (PON1) could prevent modification of LDL apoproteins by N-homocysteinylation.


5. Hcy increases oxidative stress by induction of NADPH oxidase and xanthine oxidase; and by eNOS uncoupling (BH4).

6. Hcy-NO* adduct inhibits the hydrolysis of ADMA leading to inhibition of eNOS.

7. Endothelial cells lack the ability to metabolize Hcy through transsulfuration pathways.

Uric Acid

“The available evidence has established a link between hyperuricemia and cardiovascular disease and this may be causal.”

Krishnan E, Sokolove J. *Curr Opin Rheumatol* 2010 Dec 21. [Epub]

“... a significant association between hyperuricemia (SUA ≥ 7mg/dL) and MTHFR 677T allele carriers was observed.”

“Are you using Fish Oils?”
Sudden Cardiac Death

The GISSI–Prevenzione Trial, “a recent large-scale, open-label, randomized, controlled trial in 11,324 myocardial infarction (MI) survivors has shown low-dose fish oil, but not vitamin E, to reduce significantly the cumulative rate of all-cause death, nonfatal MI, and nonfatal stroke.”

HS-Omega-3 Index

A measure of the amount of EPA+DHA in red blood cell membranes expressed as the percent of total fatty acids.

There are 64 fatty acids in this model membrane, 3 of which are EPA or DHA

\[
\frac{3}{64} = 4.6\%
\]

HS-Omega-3 Index = 4.6%

Risk for Primary Cardiac Arrest and Red Blood Cell EPA+DHA Level

90% reduction in risk
*p<0.05 vs Q1

Midrange RBC EPA+DHA by Quartile

Adapted from Siscovick DS et al. JAMA 1995;274:1363-1367.
HS-Omega-3 Index Risk Zones

Relative Risk for Death from CHD

USA/EU

Japan

Undesirable Intermediate Desirable

4% 8%

Percent of EPA+DHA in RBC

“Altogether, these results demonstrate that DHA, via its action on MAP kinases, modulates the expression of transcription factors. These results also explain the mechanism of action of this fatty acid on T-cell differentiation in disease and health.”

DHA, Not EPA, Lowers BP and HR in Humans

“The results of this study suggest that DHA is the principal omega3 fatty acid in fish and fish oils that is responsible for their BP- and HR-lowering effects in humans.”

Mori TA et al. HTN 1999;34(2):253-60.
Recent Results

Caveats:
- 4 tx arms: 226 mg EPA/150 mg DHA, 1.9 ALA, both or placebo
- Subjects with MI up to 10 years prior to entrance (not comparable to GISSI (3 months) or OMEGA (1 year)
- Average age: 69 (79% males): older and more men than GISS, GISSI-HF, and JELIS
- Subjects (also in OMEGA) on statins: only 5% in GISSI
- No change in Triglycerides in treatment groups.
- Trend to significance for reduction risk for ALA female group.
- Post-hoc, significant reduction for DM group on Fish Oils (results similar to GISSI)
- 2X2 factorial design (comparison Fish Oil, Fish Oil/ALA groups v. Placebo, Placebo/ALA groups

A Conservative Opinion

“We recommend one serving (200-400 g) of fatty fish two times per week and a diet that includes foods rich in ALA for the primary prevention of cardiovascular disease. We recommend one serving (200-400 g) of fatty fish or a fish oil supplement containing 900 mg of EPA + DHA every day and a diet rich in ALA for patients with known cardiovascular disease or congestive heart failure.”

# Fish Oil Recommendations

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficiency States (HS-Omega-3 &lt; 5%)</td>
<td>3-4 grams EPA/DHA daily</td>
</tr>
<tr>
<td>Maintenance (HS-Omega-3 &gt; 5%)</td>
<td>2 grams EPA/DHA daily</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>2-3 grams EPA/DHA daily</td>
</tr>
<tr>
<td>Autoimmune Disease</td>
<td>3-4 grams EPA/DHA daily</td>
</tr>
</tbody>
</table>

**Pearls:**
- Monitor HS-Omega-3 interval regularly
- Quality Fish Oils important – absorption, pesticides, toxic elements.
- Recommend eating fish 2-3 times weekly.
- Proportionally greater EPA for inflammatory conditions and DHA for CV/Neuro indications
“What about Insulin Resistance?”
Pathophysiology of Hyperglycemia

- Small Intestine: Digestion of Polysaccharides
- Liver: Increased Glucose Production
- Pancreas: Impaired Insulin Secretion
- Adipose tissue: Increased FFA
- Skeletal Muscle: Decreased Glucose Uptake and Utilization

Hyperglycemia
Pathophysiology of Hyperglycemia

Small Intestine: 
Digestion of Polysaccharides
- a-Glucosidase Inhibitors

Liver: 
Increased Glucose Production
- Biguanides
- Thiazolidinediones

Hyperglycemia
- Thiazolidinediones
  - Adipose tissue: Increased FFA
- Biguanides
- Thiazolidinediones
- Meglitinides

Pancreas: 
Impaired Insulin Secretion
- Sulfonylureas

Skeletal Muscle:
Decreased Glucose Uptake and Utilization
- Biguanides
- Thiazolidinediones
Pathophysiology of Hyperglycemia

**Liver:**
*Increased Glucose Production*

**Small Intestine:**
*Digestion of Polysaccharides*

**Fiber (soluble/insoluble)**
*Low-GI foods*

**Liver:**
*Hyperglycemia*

**Small Intestine:**
*Decreased Insulin Binding/Receptor “Receptiveness”*

**Pancreas:**
*Impaired Insulin Secretion*

**Antioxidants**

**Skeletal Muscle:**
*Decreased Uptake and Utilization*

**Beta Cell Destruction**

**Skeletal Muscle:**
*Exercise*

**Chromium**

**Vanadium**

**Alpha-lipoic acid**

**Omega-3 fatty acids**

**Vitamin D**

**Skull**

**Muscule**

**Decreased Glucose Uptake and Utilization**

**Beta Cell Destruction**

**Vitamin D**

**Exercise**

**Chromium**

**Magnesium**

**Vitamin C, E**

**Biotin**

**Impaired Insulin Secretion**

**Vitamin D**

**Antioxidants**
Pathophysiology of Hyperglycemia

**Small Intestine:** Digestion of Polysaccharides
- Glucomannan, Guar, Fenugreek, Touchi Extract, Mulberry

**Hyperglycemia**

**Liver:**
- Increased Glucose Production

**Systemic Inflammatory Signaling**
- RIAA/Acacia

**Green tea**

**Pancreas:**
- Impaired Insulin Secretion
- Decreased Glucose Uptake and Utilization
- Beta Cell Destruction

**Impaired Insulin Binding/Receptor “Receptiveness”**

**Small Intestine:** Digestion of Polysaccharides

**Skeletal Muscle:**
- Decreased Insulin Binding/Receptor “Receptiveness”
- Decreased Glucose Uptake and Utilization

**Cinnamon RIAA/Acacia**

**Green tea**
- Cinnamon
- Gymnema
- Aloe, Panax
- Momordica

**Ivy Gourd**

**Fenugreek**
- Cinnamon
- Banaba
- RIAA/Acacia

**IFM**
IR Signaling Cascade

- Glucose
  - Glucose transporters (GLUT)
  - GLUT vesicle
- Insulin
  - Insulin Receptor (IR)
  - TNF-α, excessive lipid (lipotoxicity)
- Extracellular
- Intercellular
  - G-protein
  - GDP
  - GTP
  - PI3K
  - PDK1
  - Akt/PKB
  - Glycogen Synthase
  - GSK-3
- Dietary phytochemicals that modulate these pathways:
  - Cinnamon
  - Berberine
  - Ginseng
  - Green Tea
  - Hops
  - Quercetin
  - Resveratrol

Nucleus
Shared Mechanisms

Beyond lipid disturbances, treating insulin resistance normalizes vascular endothelial responses.

Shear stress → PI3K → PKCβ → Akt → eNOS → Vasodilation

Dimmeler S et al. 1999.
Recommendations

• Glucomannan (or other soluble fibers at equivalent dosage) 1000 mg before meals.
• Morus indica (dried mulberry leaves) 3 grams twice daily.
• Touchi Extract (fermented soy bean – black bean sauce) 300 mg before meals three times daily.
• Panax quinquefolium (American ginseng) 3 grams before meals.
• Alpha-lipoic Acid 300-600 mg daily for diabetic neuropathy.
• Myo-inositol 2 grams twice daily for metabolic syndrome.
• RIAA/Acacia 150mg/30mg twice daily.

“What is Metabolic Cardiology?”
Sources of Nitrites and Nitrates

“Approximately 80% of dietary nitrates are derived from vegetable consumption; sources of nitrites include vegetables, fruit, and processed meats.”


“Repletion of biological nitrite and nitrate by these extracts and providing a natural system for NO generation in both endothelium-dependent and independent mechanisms may account for some of the therapeutic effects of TCMs.”

Mitochondria – Integrating Signals

“Proteins long known to drive mitochondrial fusion and fission are now reported to have emergent functions in intracellular calcium homeostasis, apoptosis, and vascular smooth muscle cell proliferation, all key issues in cardiac disease. Moreover, mitochondrial fusion has been demonstrated to be required for normal myofibril organization in skeletal muscle, and decreasing fission may confer protection against ischemic heart disease.”

Energy Metabolism

“Treatment options that incorporate metabolic interventions targeted to preserve energy substrates (D-ribose) or accelerate ATP turnover (L-carnitine and coenzyme Q10) are indicated for at risk populations or patients at any stage of CHF.”

- Ribose 5 grams 3 times daily
- Coenzyme Q10 240 mg per day
- L-carnitine 4-6 grams per day

Ribose

“D-ribose, a natural occurring carbohydrate, has demonstrated significant enhancing abilities in replenishing deficient cellular energy levels following myocardial ischemia, as well as improving depressed function in numerous animal investigations. Subsequent clinical trials have further substantiated these benefits of D-ribose in patients afflicted with ischemic cardiovascular disease and those carrying the diagnosis of congestive heart failure.”

L-Carnitine

“Twenty-nine patients with a history of NYHA functional class II symptoms and ejection fraction >45% with documented grade 1 diastolic dysfunction on echocardiogram were randomized in blinded fashion to receive 1,500 mg of L-carnitine daily for 3 months in comparison to a no treatment group (31 patients). In patients with a history of diastolic heart failure, important indices of diastolic function and symptoms appear to improve with L-carnitine treatment.”

Magnesium supplementation has been shown to be associated with:

- inverse risk of CHD in men
- inverse risk of Metabolic Syndrome
- improvements in glucose and insulin metabolism
- improvements in cardiac arrhythmias

Hawthorn

- Possible weak cardiac glycoside, ACE inhibitor
- No evidence for reduction mortality
- Efficacious for mild to moderate CHF (NYHA I – III) and for HTN

Important Nutrient Interactions

- Statins, Beta-blockers, and sulfonylureas decrease Coenzyme Q-10.
- Diuretics reduce potassium and magnesium.
- Digoxin reduces magnesium.
- Metformin reduces folic acid and B12.
- Cholestyramine decreases absorption of fat soluble vitamins and minerals.
Supplementary Assessment

Common ingredients and nutritional supplements and their relative health benefits. Larger, darker circles indicate greater likelihood that the supplement helps.

- **Blood pressure**
- **Cholesterol**
- **Diabetes**
- **Heart arrhythmias**
- **Heart disease**
- **Heart health**
- **Hypertension**
- **General cardiovascular health**

- **Cinnamon**
- **Prickly pear**
- **Bitter melon**
- **Vitamin B12**
- **Vitamin B7**
- **Magnesium**
- **Fish oil**
- **Vitamin D**
- **Red yeast rice**
- **Cocoa**
- **Black tea**
- **Green tea**
- **Milk thistle**
- **Grape skin**
- **Omega-3 fatty acids**
- **Omega-6 fatty acids**
- **Potassium**
- **Vitamin E**
- **Arginine**
- **Magnesium**

Adapted from www.informationisbeautiful.net/play/snake-oil-supplements/

A patient today ...

43 year old white male presents with recently diagnosed hypertension and reluctance to take pharmaceuticals.

- FHx premature CAD, no exercise, SAD w/45 grams EtOH daily
- BP 142/92, BMI 28, Waist 42 inches
- TC 242 mg/dl, TG 185 mg/dl, HDL 36 mg/dl, LDL 169 mg/dl, Glucose 104 mg/dl, Insulin 22 µU/ml

Dx: **Metabolic Syndrome** (5 of 5)

Mechanisms:
- Oxidative Stress/Energy Production
- Neuro-endocrine signaling
- Antecedents: nutritional deficiencies/genetics
- Social beliefs
<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Always (YES/NO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIA</td>
<td>Yes</td>
</tr>
<tr>
<td>GGT</td>
<td>Yes</td>
</tr>
<tr>
<td>Urinary Toxic Elements (Provoked Timed Collection)</td>
<td>No</td>
</tr>
<tr>
<td>25(OH) and 1,25 di(OH) Vitamin D₃</td>
<td>Yes</td>
</tr>
<tr>
<td>Omega 3 Index</td>
<td>Yes</td>
</tr>
<tr>
<td>hs CRP</td>
<td>Yes</td>
</tr>
<tr>
<td>PLAC (phospholipase A2)</td>
<td>No</td>
</tr>
<tr>
<td>Cardiogenomics panel</td>
<td>No</td>
</tr>
<tr>
<td>Thyroid status/Hormonal Status</td>
<td>Yes</td>
</tr>
<tr>
<td>Digestive and Stool Analysis</td>
<td>No</td>
</tr>
<tr>
<td>Gluten Auto-antibodies</td>
<td>No</td>
</tr>
</tbody>
</table>
What I prescribe...

First Line
- Soy-based Medical Food with Actives
- Fish Oil
- 5000 iu Vitamin D₃
- Mediterranean-style LGL food plan
- Exercise
- Mind-Body-Spirit Practice

Second Line
- Extended Release Niacin
- Coenzyme Q10 (>100 mg)
- Detox Support
- Probiotic (Lactobacillus acidophilus NCFM)
- 5-MTHF
- Hormonal Support
“Do not go where the path may lead, go instead to where there is no path and leave a trail.”

Ralph Waldo Emerson