A Integrative Medicine Approach to Cardiometabolic Syndrome

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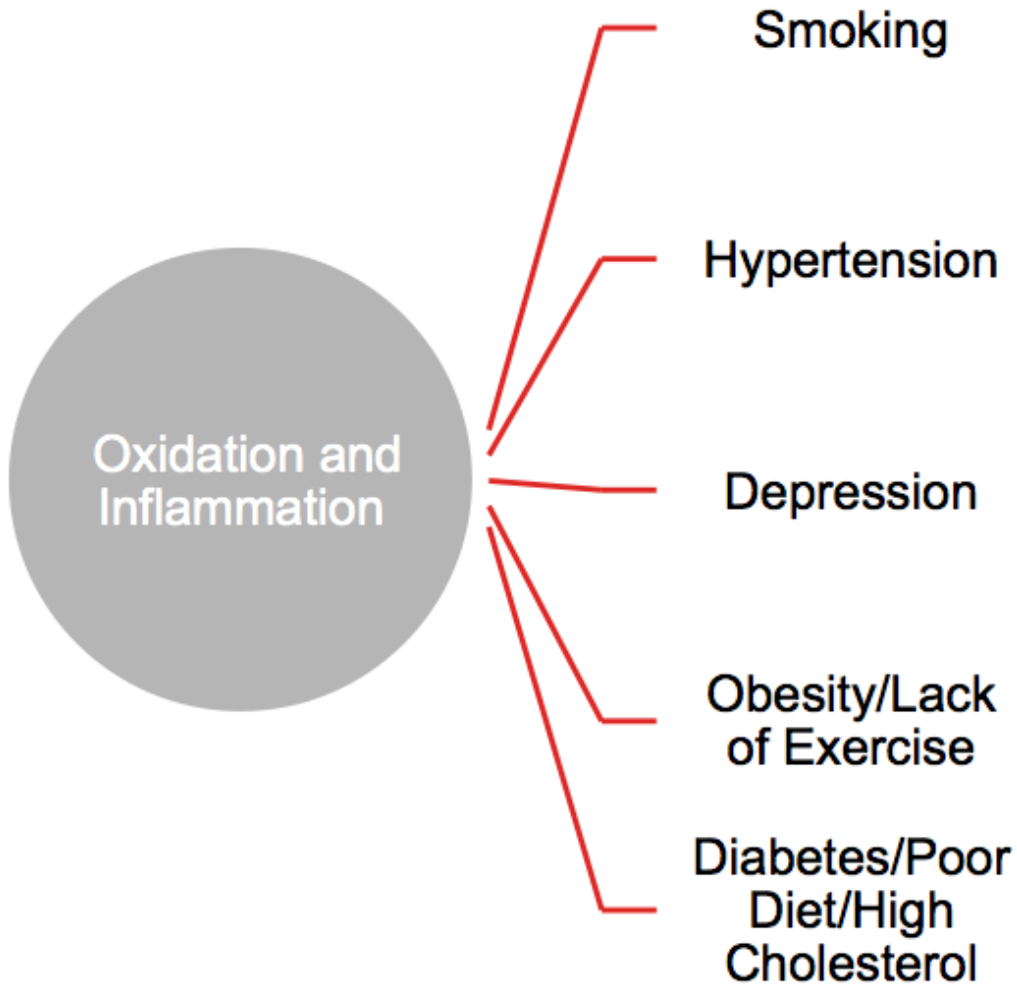
Inflammation

FEBR. 2004

WHAT DO ALL THE AHA RISK FACTORS HAVE IN COMMON?



Sugar on Fire

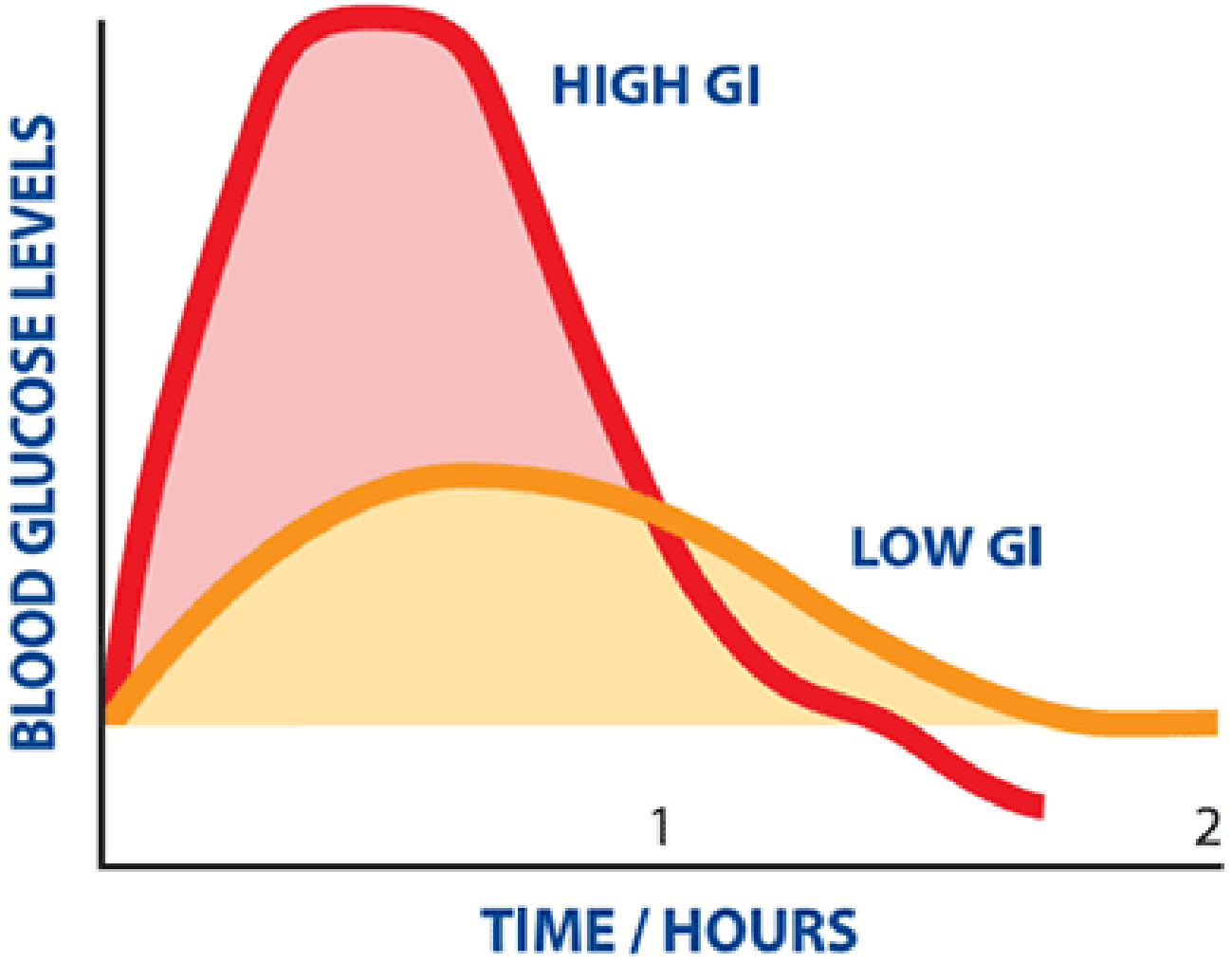
Glucotoxicity

structural and functional damage to beta cells *and* target tissues caused by chronic hyperglycemia.

Causes insulin resistance

Lipotoxicity

damage caused by high free fatty acid levels



The amount of carbohydrate in the reference and test food must be the same.





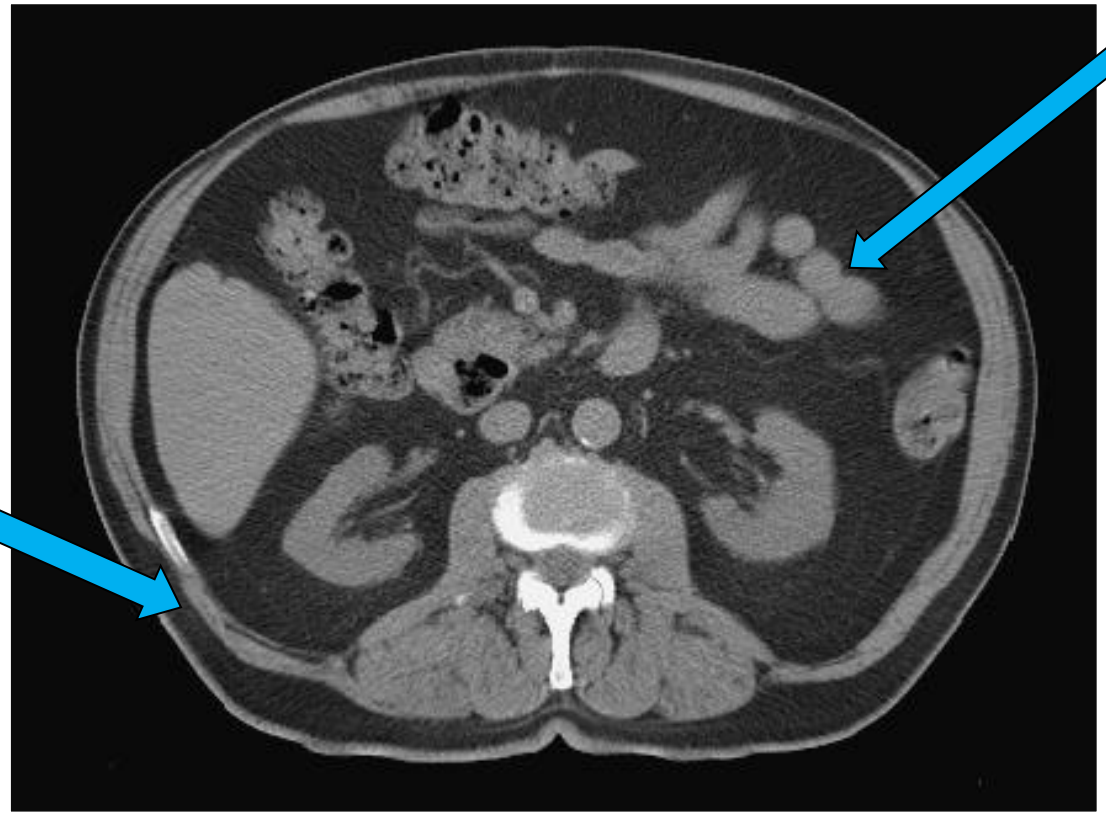


Diabetes and Inflammation on the Attack

Glycosylation= Caramelize our Cells

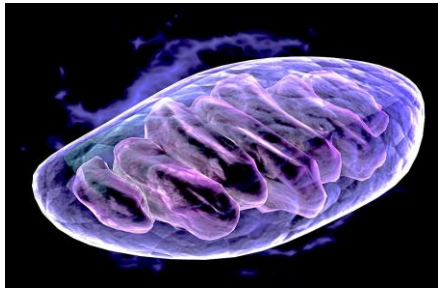
External Fat vs. Internal “Hot Fat” Adipose Tissue

Visceral Fat
(Internal “Hot” Fat)



Subcutaneous Fat
(External Fat)

Mitochondria Facts



- Mitochondria typically 5 kg of body weight
- Mitochondria are responsible for 90-95% of free radicals in our cells, thereby disrupting healthy cells.
- Mitochondria are exposed to 10x more free radicals than the rest of the cell.
- By age 30, energy production drops by up to 10% per decade leading to aging.
- Because of their high energy requirements, neurons are especially vulnerable to injury and death from dysfunctional mitochondria.
- Current evidence for mitochondrial dysfunction in all neurodegenerative diseases.

Mitochondrial Dysfunction- The Ripple Effect

Mitochondrial dysfunction is associated with over 300 adverse health conditions.

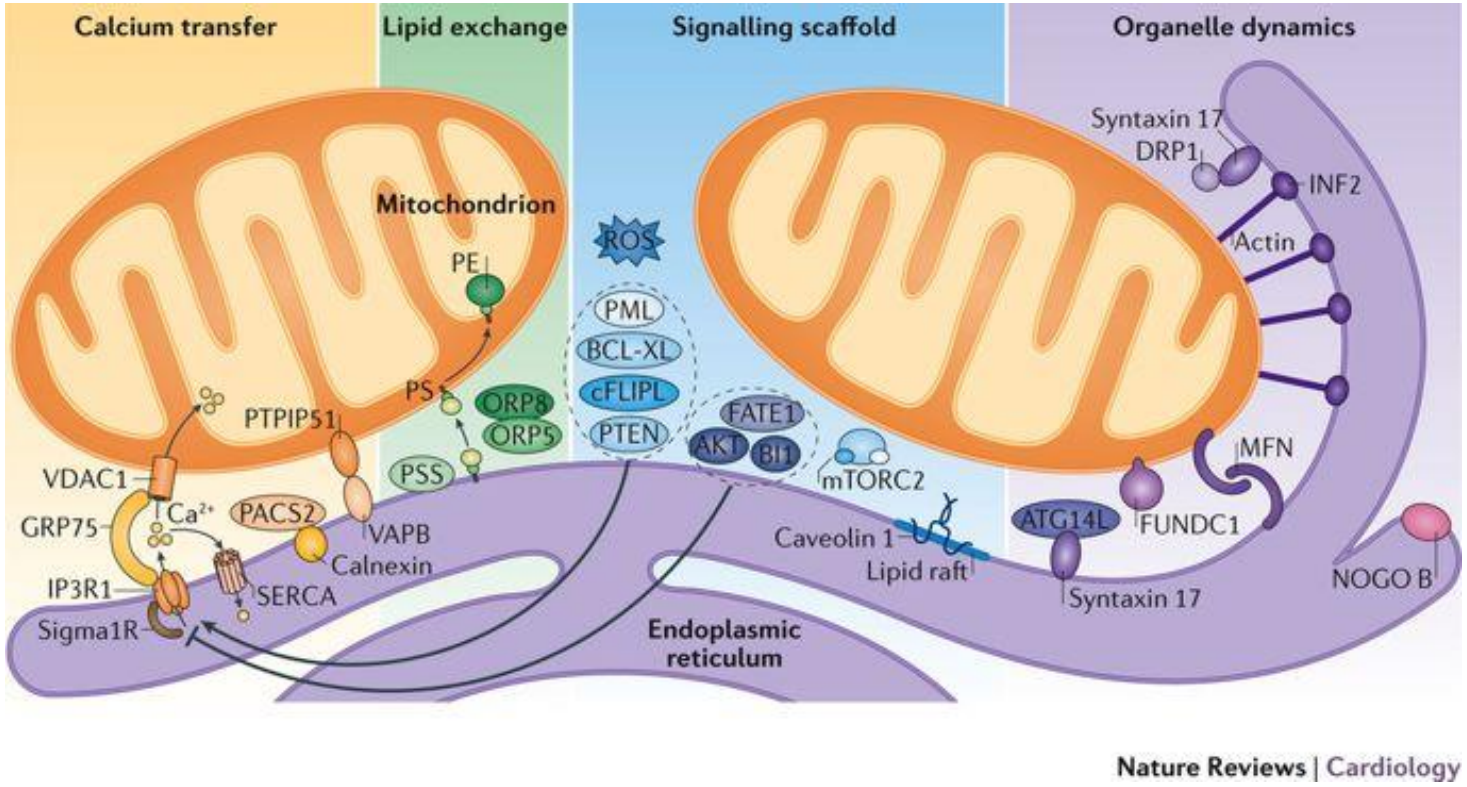
3 Types of Mitochondrial Dysfunction

- Age Related Dysfunction with gradual decline
- Primary Mitochondrial Dysfunction with suboptimal function and energy production
- Secondary Mitochondrial Dysfunction
  -Aggravated by epigenetic factors, including illness, stress, diet, lifestyle, medication

Mitochondria & Cardiovascular System

- Mitochondria are highly present in cardiac cells due to high energy demands (~35% of the volume of cardiac tissue).

- Oxidative stress is related to cardiovascular diseases.



Inflammation, defective insulin signaling, and neuronal dysfunction in Alzheimer's disease

Shared mechanisms of pathogenesis between metabolic disorders and AD.

Peripheral and central nervous system inflammation link the pathogenesis of AD and metabolic diseases.

Mitochondrial Dysfunction And Diabetes

Environmental factors, pollutants, and mitochondrial toxins in the pathogenesis of diabetes

Mitochondrial dysfunction plays a role in the pathophysiology of insulin insensitivity

Medications Linked to Mitochondrial Dysfunction

Drug Class	Medications
Alcoholism medications	Disulfiram (Antabuse)
Analgesic and anti-inflammatory	Aspirin, acetaminophen (Tylenol), diclofenac, fenoprofen, indomethacin, naproxen
Anesthetics	Bupivacaine, lidocaine, propofol
Angina medications	Perhexiline, amiodarone
Antiarrhythmic	Amiodarone
Antibiotics	Tetracycline, antimycin A
Antidepressants	Amitriptyline, amoxapine, citalopram, fluoxetine
Antipsychotics	Chlorpromazine, fluphenazine, haloperidol, risperidone, quetiapine, clozapine, olanzapine
Anxiety medications	Alprazolam (Xanax), diazepam (valium)
Barbiturates	Amobarbital, aprobarbital, butabarbital, butalbital, methylphenobarbital, pentobarbital, phenobarbital, primidone, secobarbital, thiobarbital
Cholesterol medications	**Statins** – atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin. **Bile acids** – cholestyramine, clofibrate, ciprofibrate, colestipol, colesevelam
Chemotherapy medications	Mitomycin C, profiromycin, adriamycin (also called doxorubicin and hydroxydaunorubicin and included in the following chemotherapeutic regimens – ABVD, CHOP, and FAC)
Dementia	Tacrine (Cognex), Galantamine (Reminyl)
Diabetes medications	Metformin (Glucophage), troglitazone, rosiglitazone, buformin
HIV/AIDS medications	Retrovir (AZT, ZDV, zidovudine) and several other medications
Epilepsy/Seizure medications	Valproic acid (Depacon, Depakene, Depakene syrup, Depakote, depakote ER, depakote sprinkle, divalproex sodium)
Mood stabilizers	Lithium
Parkinson's disease medications	Tolcapone (Tasmar, Entacapone (COMTan, also in the combination drug Stalevo)

*adapted from Molecular Nutrition & Food Research 2008, 52, 780-788

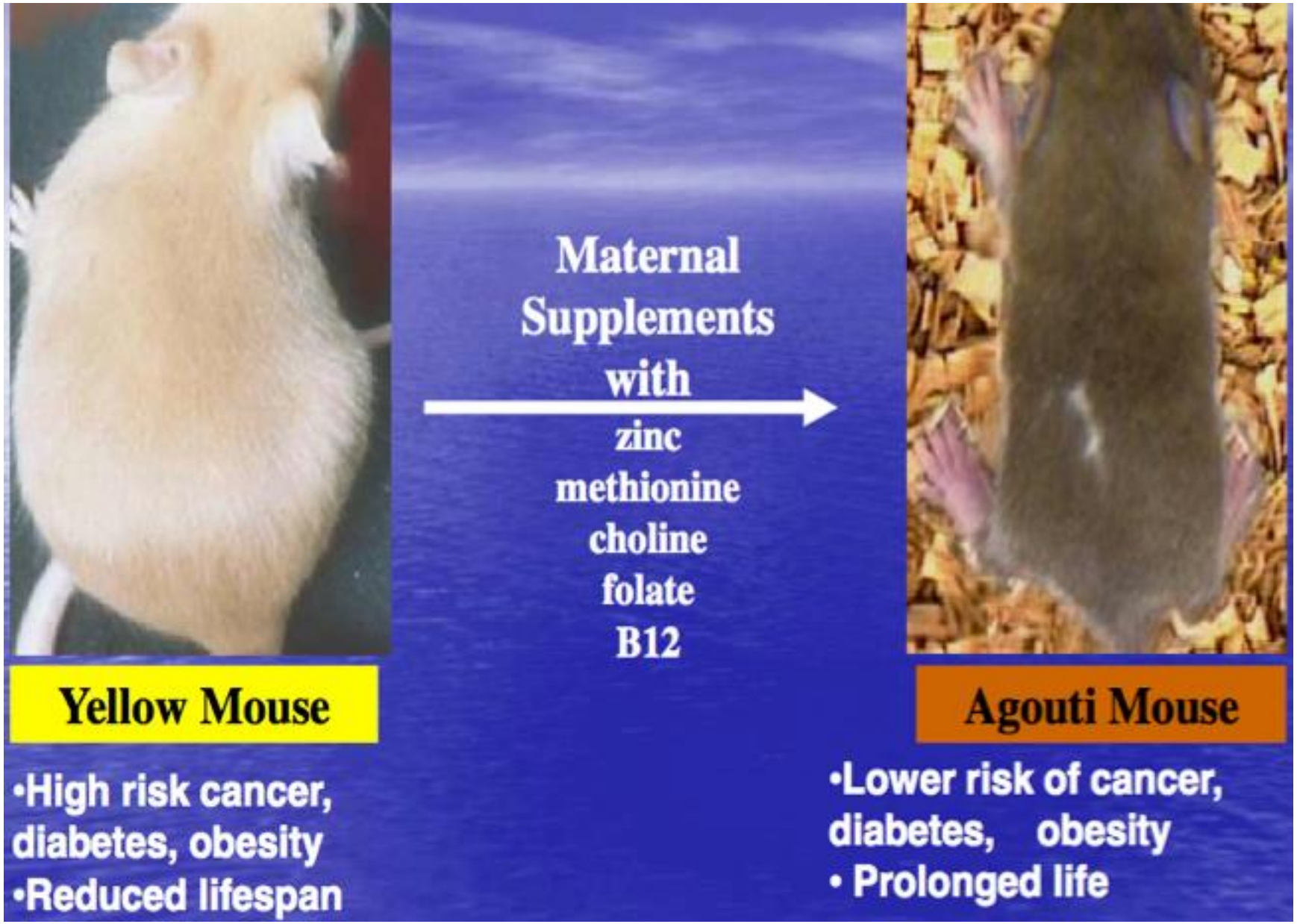
Emerging Genetic SNPs

Cardiovascular Disease	ApoE
Elevated LDL, TG	APOB
Atrial Fibrillation	PITX2
Coronary Artery Disease	HNF1A and 11
Hypertension	BCAT1and PPARGC1A
Peripheral Artery Disease	CHRNA3
Venous Thrombosis/CAD/Hormone?	Factor V Leiden
	Prothrombin G20210A (Factor II)
	?MTHFR (homocysteine)
Caffeine Metabolism	CYP1A2
Clopidogrel Metabolism (Plavix)	CYP2C19
Simvastatin-induced Myopathy	SLCO1B1
Verapamil and QTc interval	NOS1AP
Warfarin Metabolism	CYP2C9, VKORC1
Verapamil or Atenolol benefit	CACNA1C

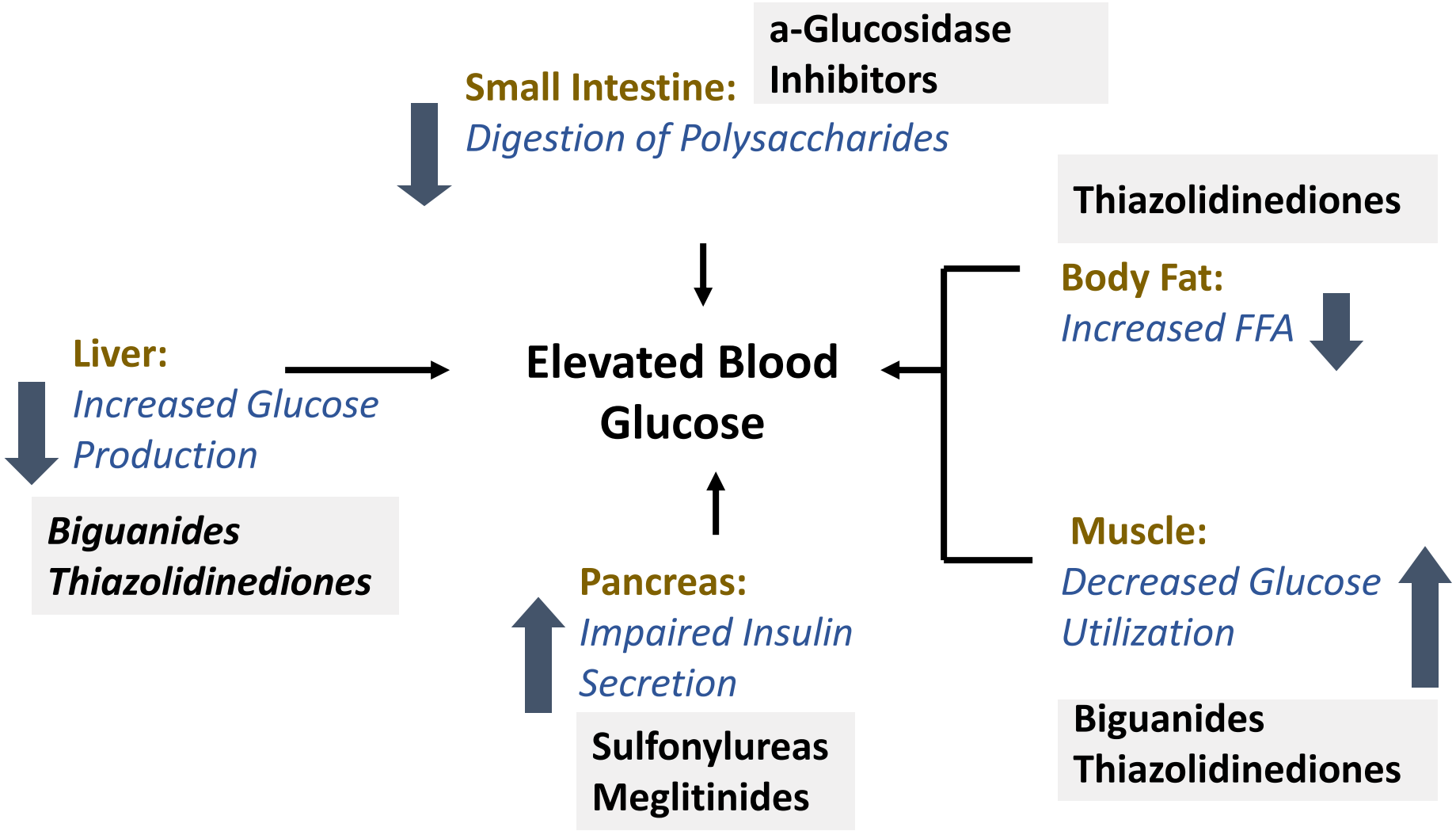
Randy Jirtle/Duke University

Hypo-methylated

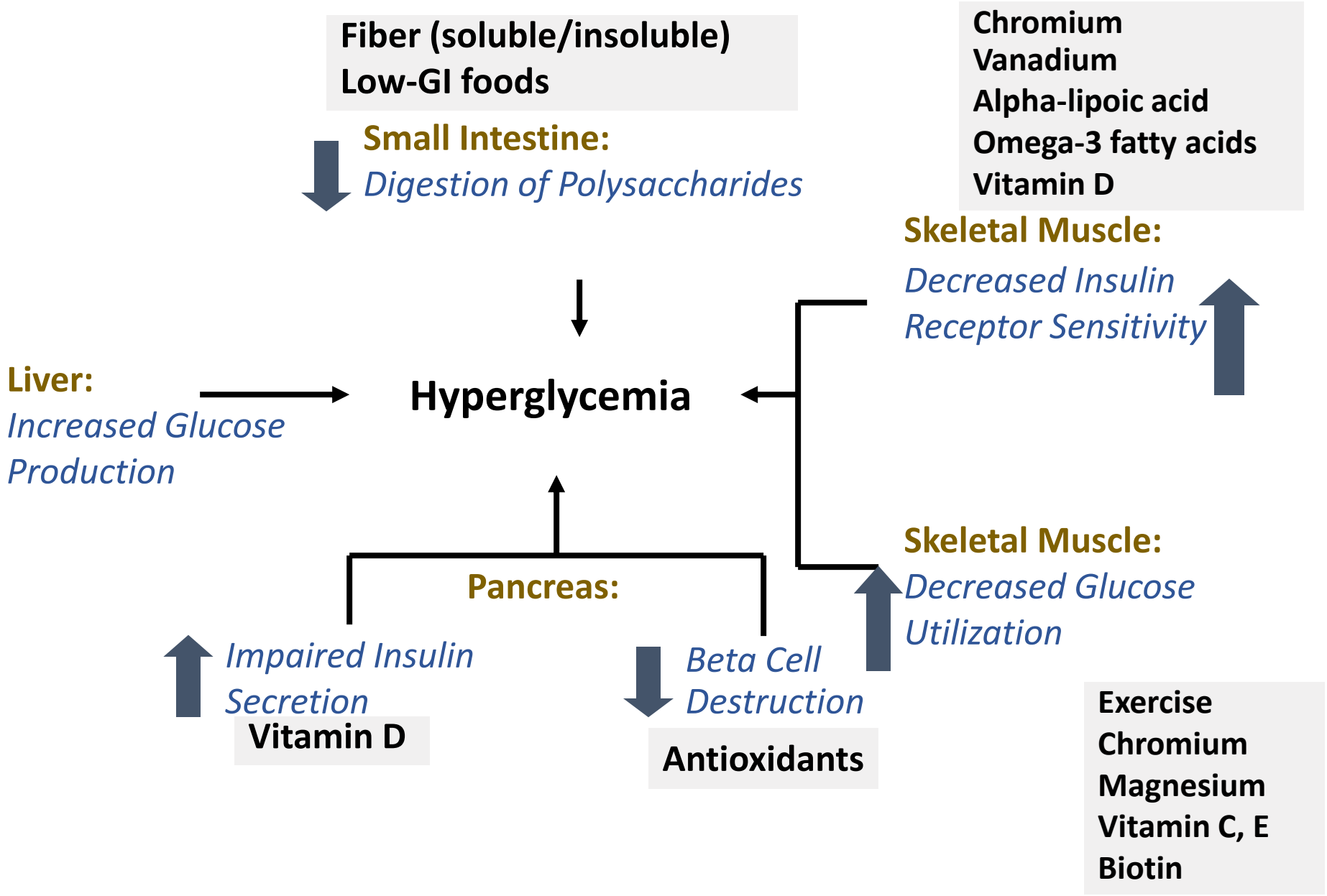
Hyper-methylated



Drug Solutions for Diabetes



Food, Supplement, Lifestyle Solutions



EDITORIAL

Statins for Primary Cardiovascular Disease Prevention
Time to Curb Our Enthusiasm

Anand R. Habib, MD, MPhil; Mitchell H. Katz, MD; Rita F. Redberg, MD, MSc

In the US, more than 126 million adults have been diagnosed with cardiovascular disease (CVD).[1] Reducing the morbidity and mortality associated with CVD is a public health imperative. Accordingly, considerable resources and effort have been invested in determining not only how to effectively treat symptomatic coronary artery disease or ischemic stroke, but also on prevention of clinical CVD. Although elevated low-density lipoprotein (LDL) is associated with higher rates of CVD,[2] there is uncertainty regarding the net benefit to risk ratio of using statins to reduce LDL among persons without CVD (primary prevention). This contrasts with the established role of LDL reduction for persons with established CVD (secondary prevention).

Multimedia

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The US Preventive Services Task Force (USPSTF) has updated its 2016 recommendations on the use of statins for the primary prevention of clinical CVD.[3] Two of us (M.H.K. and R.F.R.) wrote about the 2016 recommendations,[4] and in this Editorial we update our comments for the 2022 to experience small net benefit (C recommendation) from initiation of a moderate-intensity statin, and thus clinicians should engage patients in shared decision-making. Third, the Task Force concludes that there is insufficient evidence (I statement) to fully assess the net harms and benefits of initiating statins in adults 76 years and older, regardless of estimated 10-year CVD event risk or presence of risk factors.

The details of the updated recommendations merit further consideration.[5] The systematic review[6] that accompanies the 2022 USPSTF recommendations examined 22 randomized clinical trials (RCTs; n = 90 624 participants) that compared statin therapy vs placebo or no statin, with a mean follow-up duration of 3 years. The systematic review examined the clinical end points of all-cause mortality, CVD mortality, fatal/nonfatal myocardial infarction, and fatal/nonfatal stroke among those with a mean age of 52 to 66 years, except for 1 trial that only enrolled older individuals between 70 and 82 years of age (**Table**[6,7]).

The updated evidence synthesis[6] found that statins yielded a slightly smaller, but still statistically significant, reduction in all-cause mortality (pooled relative risk, 0.92; 95% CI, 0.87-0.98), as well as for myocardial infarction and stroke (Table)

EDITORIAL

Statins for Primary Prevention
The Debate Is Intense, but the Data Are Weak

Rita F. Redberg, MD, MSc; Mitchell H. Katz, MD

A recent issue of *JAMA* contains the latest US Preventive Services Task Force (USPSTF) recommendation statement on statins for prevention of cardiovascular disease in adults,[1] along with the accompanying evidence report and systematic review[2] on which the recommendations are based. The evidence report summarized data from 19 trials including a total of 71 344 patients and concluded that statin therapy was associated with reduced risk of all-cause and cardiovascular mortality and cardiovascular disease (CVD) events. Thus, the task force recommended "initiating use of low- to moderate-dose statins in adults aged 40 to 75 years without a history of CVD who have 1 or more CVD risk factors and a calculated 10-year CVD event risk of 10% or greater (B recommendation)" or "7.5% to 10% (C recommendation)."[1] Although the task force did their usual careful job of reviewing the evidence, the evidence for treating asymptomatic persons with statins does not appear to merit a grade B or even a grade C recommendation.

Related articles at jama.com

The task force evidence report estimated an absolute bentential bias, all of the trials included in the task force evidence report[2] were industry-sponsored except 1 trial,[5] and that trial contributed 0.2% of the weight to the mortality calculation. Industry-sponsored studies have been shown to report greater benefit and lesser adverse effects than noncommercially sponsored trials of the same drugs.[6] Whether this is true for statins and primary prevention of CVD is unknown.

Among the 19 randomized clinical trials of statins vs placebo or no statin included in the evidence report for the task force recommendations, only 15 reported all-cause mortality, 10 reported cardiovascular mortality, 12 reported fatal and nonfatal myocardial infarction, and 13 reported fatal and nonfatal stroke.[2,7] Reliance on selective reporting of the most important outcomes, which are likely included in the clinical trial data, makes reporting bias possible. Furthermore, after all-cause mortality, the comparative incidence of serious adverse events between treatment and control groups is arguably the second most important measure of the effect of active therapy in randomized clinical trials.

Understanding the evidence base in evaluating harms of

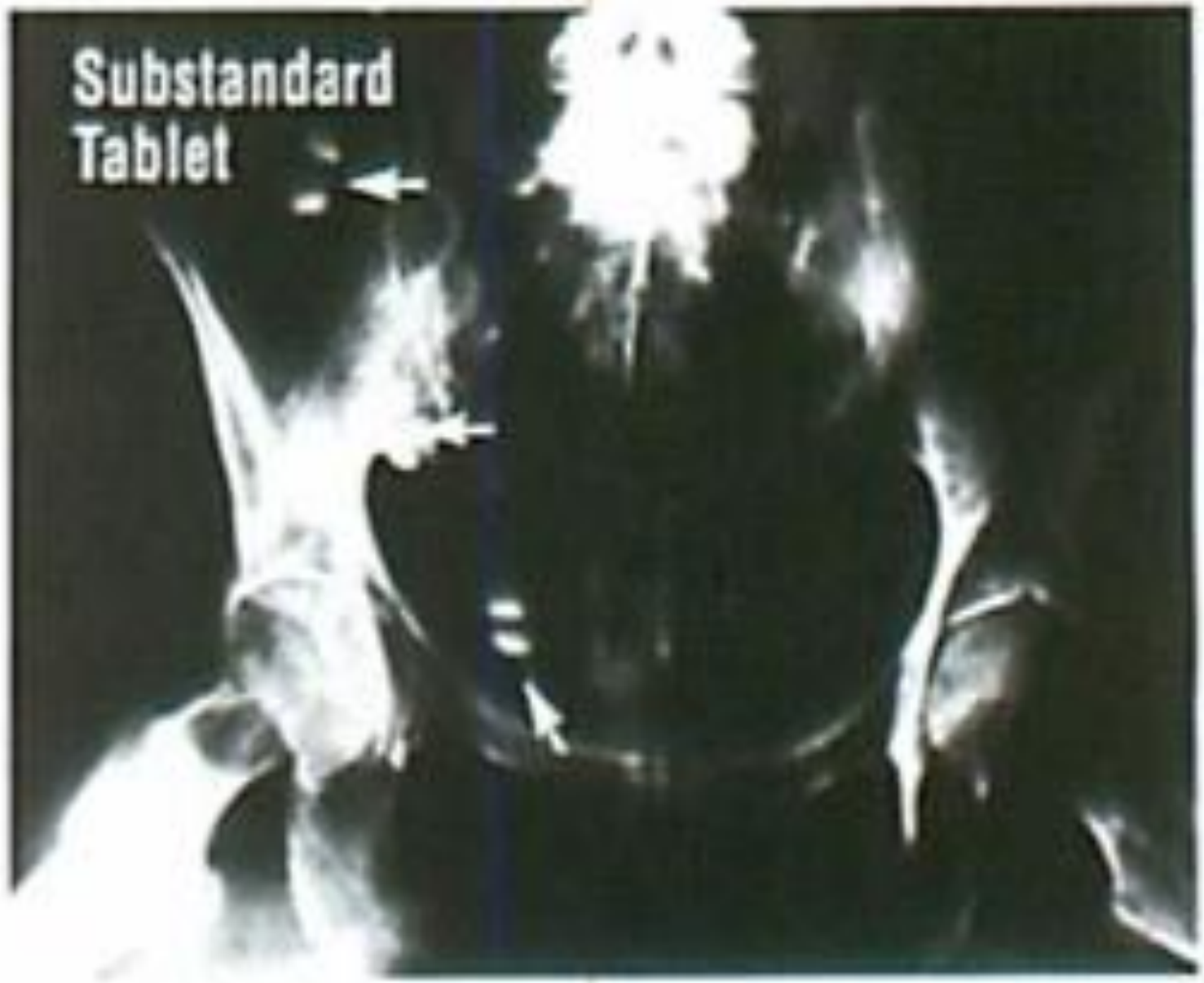
Probiotics As Beneficial Agents In The Management Of Diabetes Mellitus

Probiotics have beneficial effects on glycemic controls

- fasting plasma glucose
- postprandial blood glucose
- HgbA1C
- insulin
- insulin resistance
- onset of diabetes

Lifestyle As An Intervention


WaterCrystal
Cradle
Turmeric
500 mg
equate
Calcium
Citrate+
Dietary Supplement
TWIN
SPRING
Cinnamon
500 mg
Plus Chromium
Dietary Supplement
SPRING
Flush Free
Niacin
500 mg
HEART HEALTH
Dietary Supplement
SPRING
Alpha
VALLEY


Substandard
Tablet

Common Obstacles:

Cost

Time

Portions and Serving Size

Good fat vs Bad fat

Bread = Soda pop

Juice = Soda pop (alternatives)

Water intake ½ oz per lb body wt

- **Mineral water with fruit slices**
- **Unsweetened herbal teas**

Sleep less than 7 hours per night

Sleep apnea

Nocturnal hypoxia

Insomnia

Frequent awakening

Sleeping late

Stress-related sleep disorders

Food - low glycemic foods

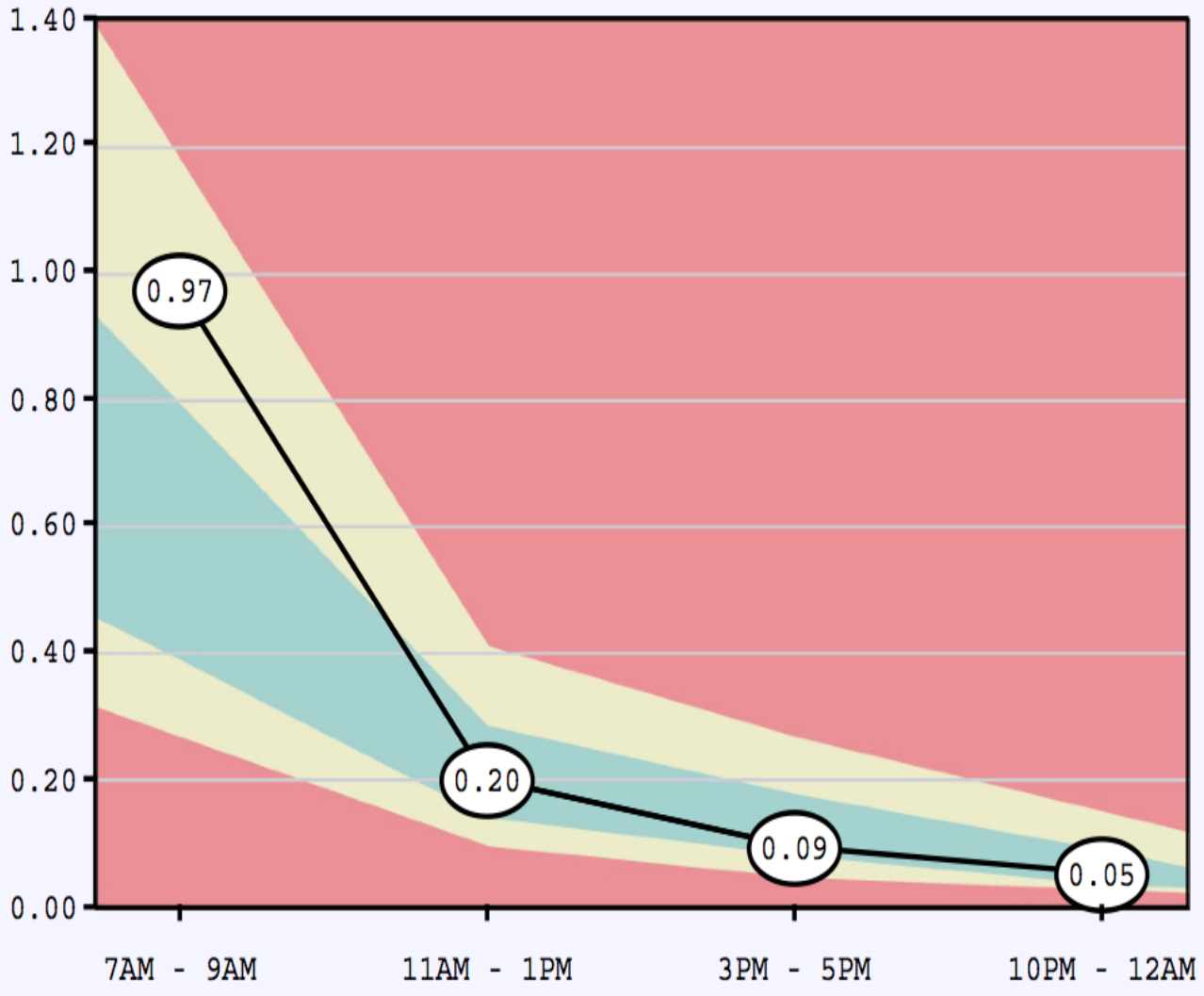
Lifestyle - moderation in exercise, ‘recovery exercise’

Routines with sleep and ‘down time’

Clean food**, clean** water**, clean** air

EWG.org - clean fifteen, dirty dozen foods

Salivary Cortisol and DHEA



Cortisol♦

Reference Range

1 Hour After Rising
7AM - 9AM:

0.27-1.18 mcg/dL

11AM - 1PM:

0.10-0.41 mcg/dL

3PM - 5PM:

0.05-0.27 mcg/dL

10PM - 12AM:

0.03-0.14 mcg/dL

Figure 1: heart rhythms when stressed

When you are experiencing positive emotions such as appreciation, pattern becomes more ordered and coherent. (See graph below.)

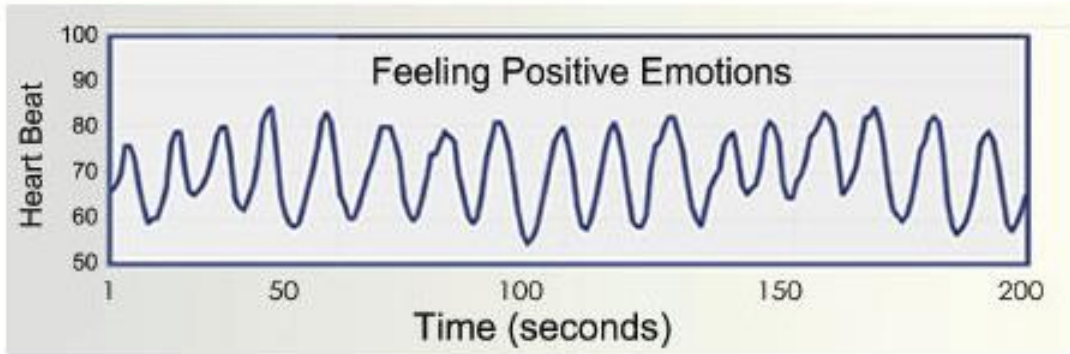


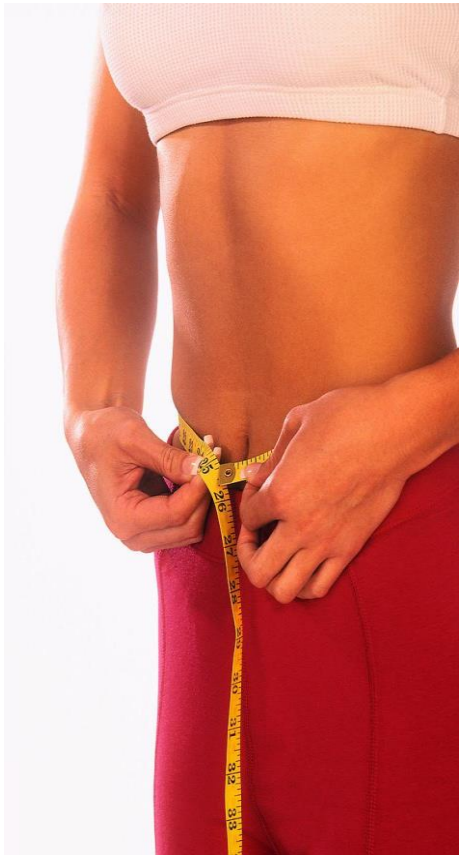
Figure 2: heart rhythms when feeling a positive emotion

Important Nutrient Interactions

- **Statins, Beta-blockers, and sulfonylureas decrease Coenzyme Q-10.**
- **Statins decrease selenium, omega 3FA, fat soluble vitamins carnitine and free T3.**
- **Beta-blockers decrease melatonin, hyperglyciem.**
- **Diuretics reduce potassium, magnesium, folate, B_6, B_{12}, thiamine, iodide and selenium.**
- **Digoxin reduces magnesium.**
- **Metformin reduces folic acid and B12.**
- **ACEI and ARB decrease zinc.**
- **Cholestyramine decreases absorption of fat soluble vitamins and minerals.**

Benefits From Detox

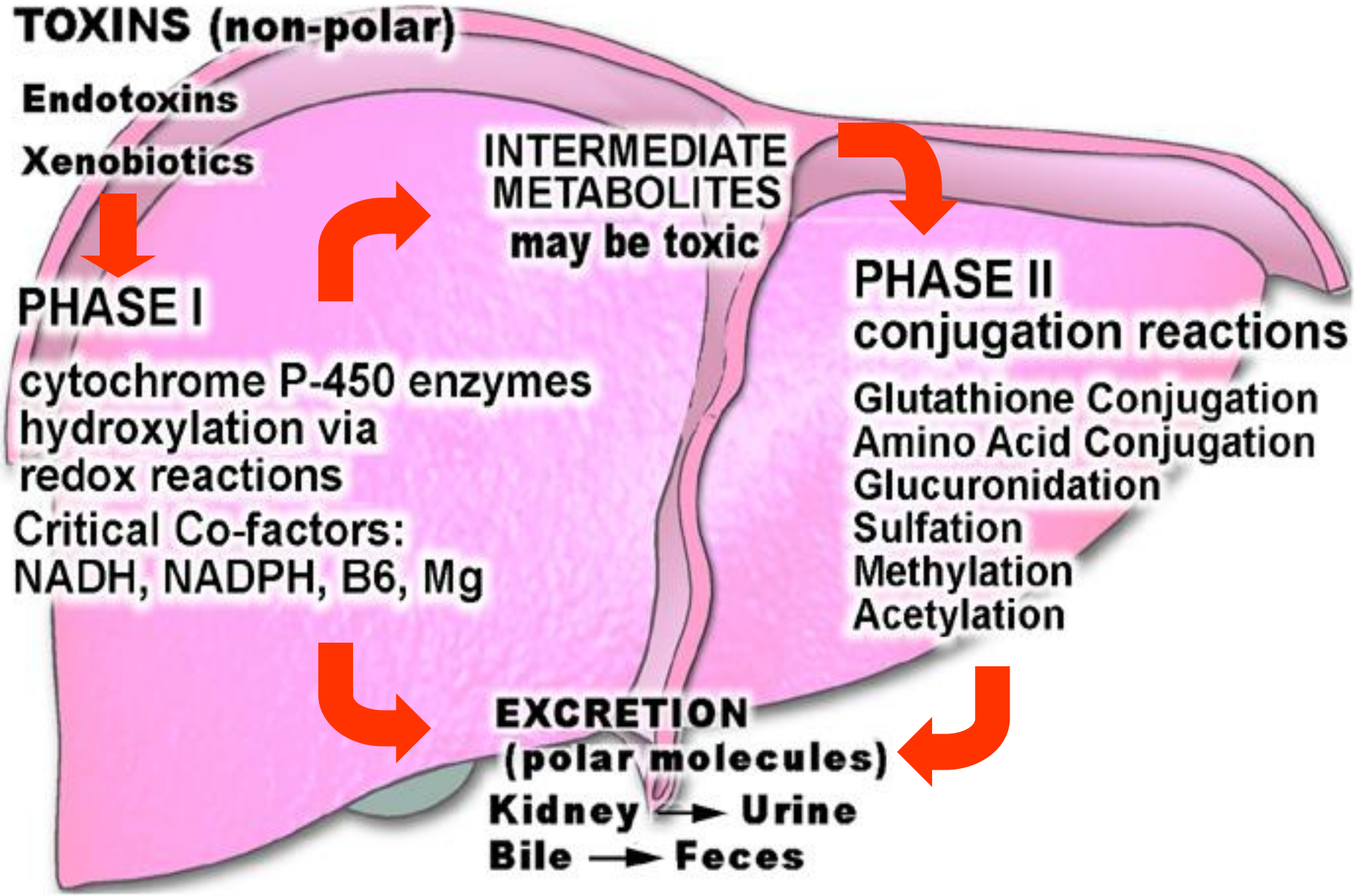
- Anti-Aging Effects
- Increased Energy
- Weight Loss
- Clearer Skin and Eyes
- Greater Motivation and Creativity
- Reduction of Allergic Symptoms



YOUR LIVER IS YOUR LIFELINE

- This detox protocol was designed to focus on the liver – the body's primary organ of detoxification – and the bowel.
- Your liver filters 2 quarts of blood every minute.
- It also makes and secretes bile to break down fats and transport toxins out via the bowel.
- The liver disassembles and neutralizes unwanted chemicals, usually in two steps referred to as *Phase I* and *Phase II* .

LIVER DETOXIFICATION



Categories of Toxicants

Pesticides
- Insecticides
- Herbicides

Combustion / Incineration Pollutants

Synthetic Medications

Food Additives and preparation by-products

Cosmetic Additives

Industrial Compounds and Chemical Byproducts
- Volatile organics such as solvents and detergents
- Toxic metals
- Plasticizers
- Insulators (asbestos)

POPS
Persistent Organic Polutants

Check GGT

BMI = Diabetes risk ONLY if high GGT

BPA and Diabetes link

JAMA 2008

Bisphenol A and Risk of Metabolic Disorders

Frederick S. vom Saal, PhD
John Peterson Myers, PhD

IN THIS ISSUE OF *JAMA*, LANG AND COLLEAGUES[1] REPORT the results of the first major epidemiologic study to examine the health effects associated with the ubiquitous estrogenic chemical bisphenol A (BPA). This compound is the base chemical (monomer) used to make polycarbonate plastic food and beverage containers, the resin lining of cans, and dental sealants; it also is found in "carbonless" paper used for receipts as well as a wide range of other common household products. Based on their analysis of data from the National Health and Nutrition Examination Survey 2003-2004, Lang et al report a significant relationship between urine concentrations of BPA and cardiovascular disease, type 2 diabetes, and liver-enzyme abnormalities in a representative sample of the adult US population. This report, suggesting links between BPA and some of the most significant and economically burdensome human diseases, is based on a cross-sectional study and therefore cannot establish causality; follow-up longitudinal studies should thus be a high priority. Yet many peer-reviewed published studies report on related adverse effects of BPA in experimental animals,[2] and cell culture studies identify the molecular mechanisms mediating these responses.[3] These experimental findings add biological plausibility to the results reported by Lang et al.[1]

Based on this background information, the study by Lang et al,[1] while preliminary with regard to these diseases in humans, should spur US regulatory agencies to follow the recent action taken by Canadian regulatory agencies, which have declared BPA a "toxic chemical" requiring aggressive action to limit human and environmental exposures.[4] Alternatively, Congressional action could follow the precedent set with the recent passage of federal legislation designed to limit exposures to another family of compounds, phthalates, also used in plastic. Like BPA,[5] phthalates are detectable in virtually everyone in the United States.[6] This bill moves US policy closer to the European model, in which industry must provide data on the safety of a chemical before it can be used in products.

See also p 1303.

Subsequent to an unexpected observation in 1997, numerous laboratory animal studies[2] have identified low-dose drug-like effects of BPA at levels less than the dose used by the US Food and Drug Administration (FDA) and the Environmental Protection Agency to estimate the current human acceptable daily intake dose (ADI) deemed safe for humans. These studies have shown adverse effects of BPA on the brain, reproductive system, and—most relevant to the findings of Lang et al[1]—metabolic processes, including alterations in insulin homeostasis and liver enzymes.[2] However, no prior studies examining BPA for effects on cardiovascular function have been conducted in laboratory animals or humans.

Epidemiologists are informed by animal studies that identify potential human health hazards when the animal models and exposure levels are relevant and effects are mediated via response mechanisms present in humans. For example, when adult rats were fed a 0.2-µg/kg per day dose of BPA for 1 month (a dose 250 times lower than the current ADI), BPA significantly decreased the activities of antioxidant enzymes and increased lipid peroxidation, thereby increasing oxidative stress.[7] When adult mice were administered a 10-µg/kg dose of BPA once a day for 2 days (a dose 5 times lower than the ADI), BPA stimulated pancreatic β cells to release insulin. After administration of 100 µg/kg per day of BPA via injection or feeding for 4 days, mice developed insulin resistance and postprandial hyperinsulinemia. Follow-up studies showed that stimulation of mouse β-cell insulin production and secretion by between 0.1 to 1 nM of estradiol or BPA (23-230 pg/mL of BPA) is mediated by activation of the extracellular signal-related protein kinase 1/2 pathway by binding of BPA to estrogen receptor α and that via this nonclassical estrogen-response mechanism, BPA and estradiol have equal potency and efficacy.[8] BPA and estradiol are also equipotent at inhibiting adiponectin release from human adipocytes at 1 nM, further implicating BPA at current human exposure levels in insulin resistance and the metabolic syndrome.[9]

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Arsenic and Diabetes

Elevated mortality rates for both males and females for diabetes mellitus

And…

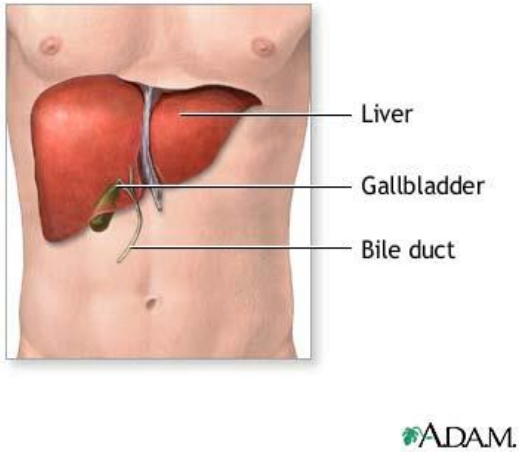
-renal disease

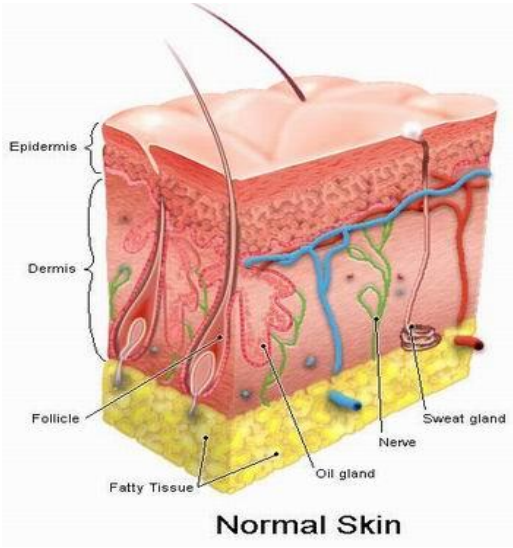
-heart disease

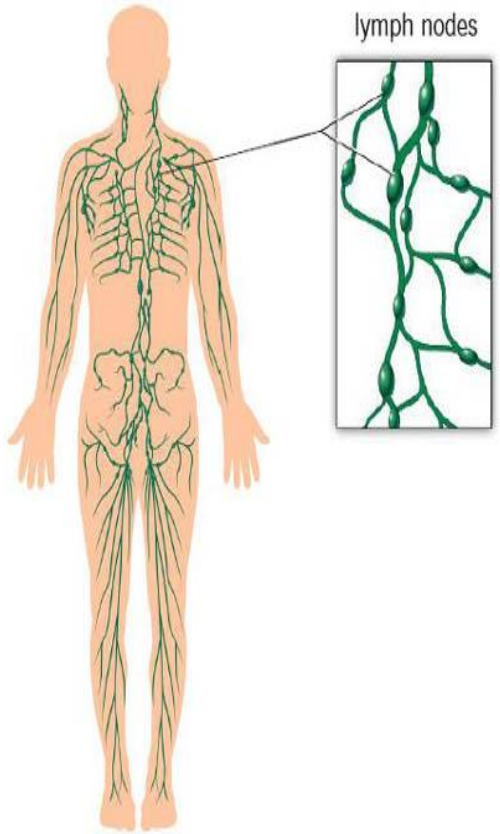
-stroke

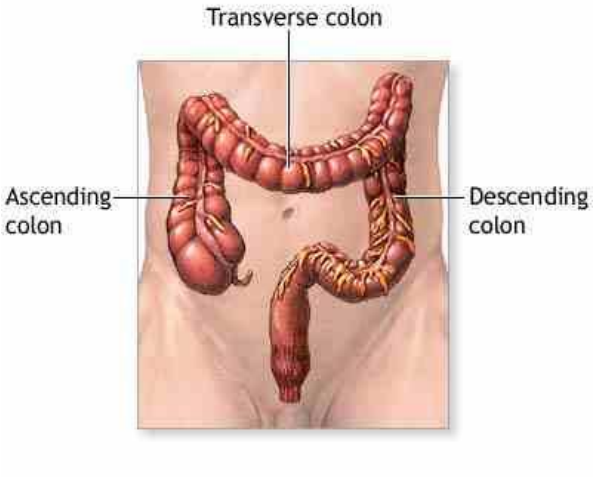
Meliker JR, et al. (2007). Environ Health.

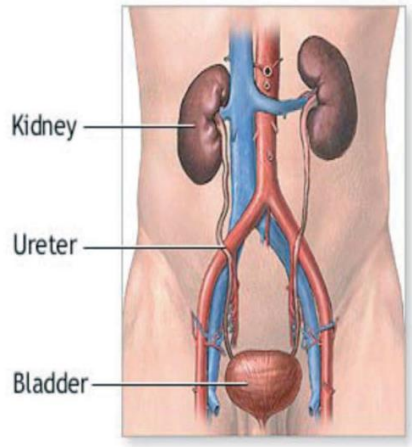
YOUR DETOXIFICATION SYSTEMS

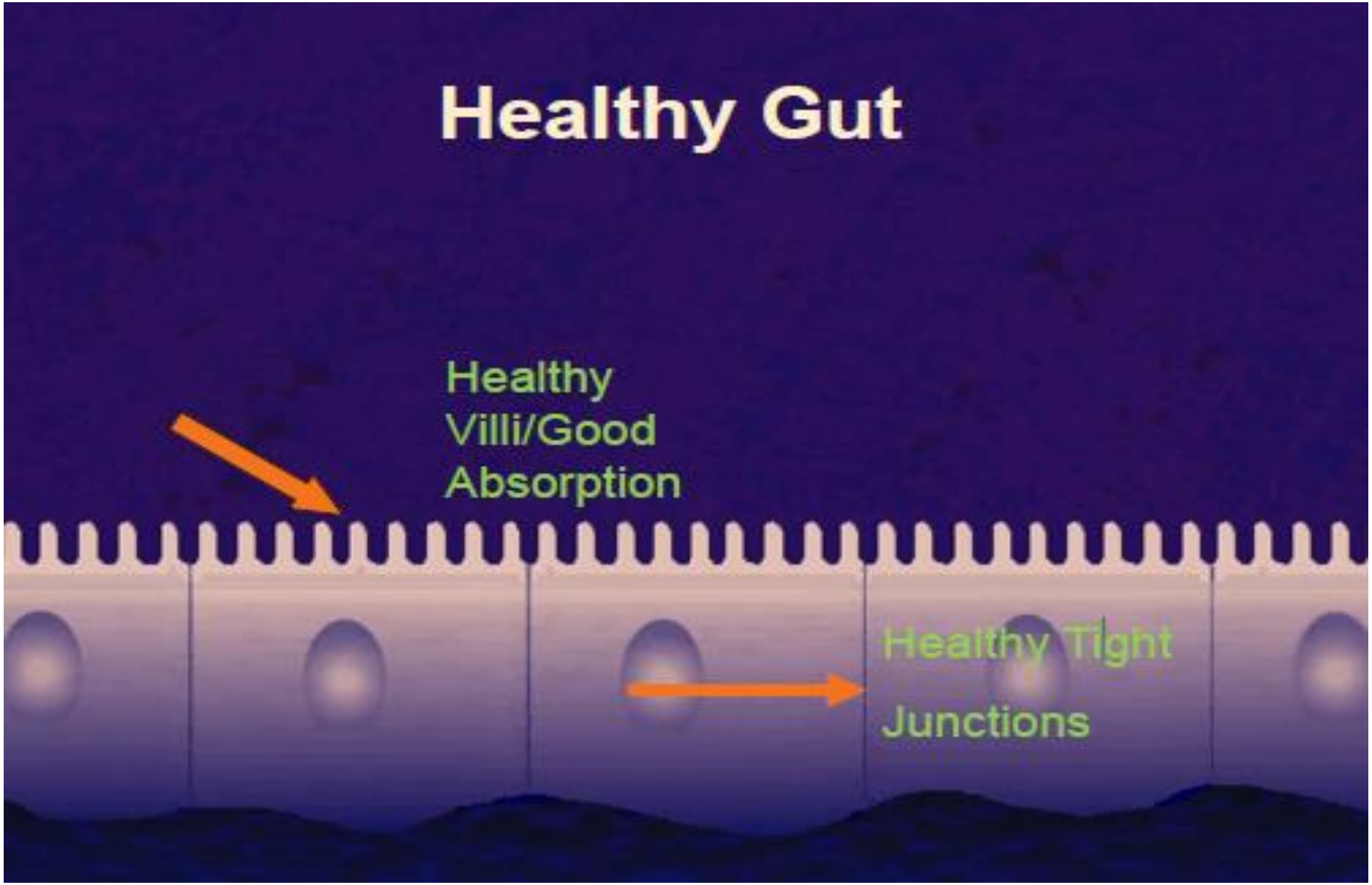


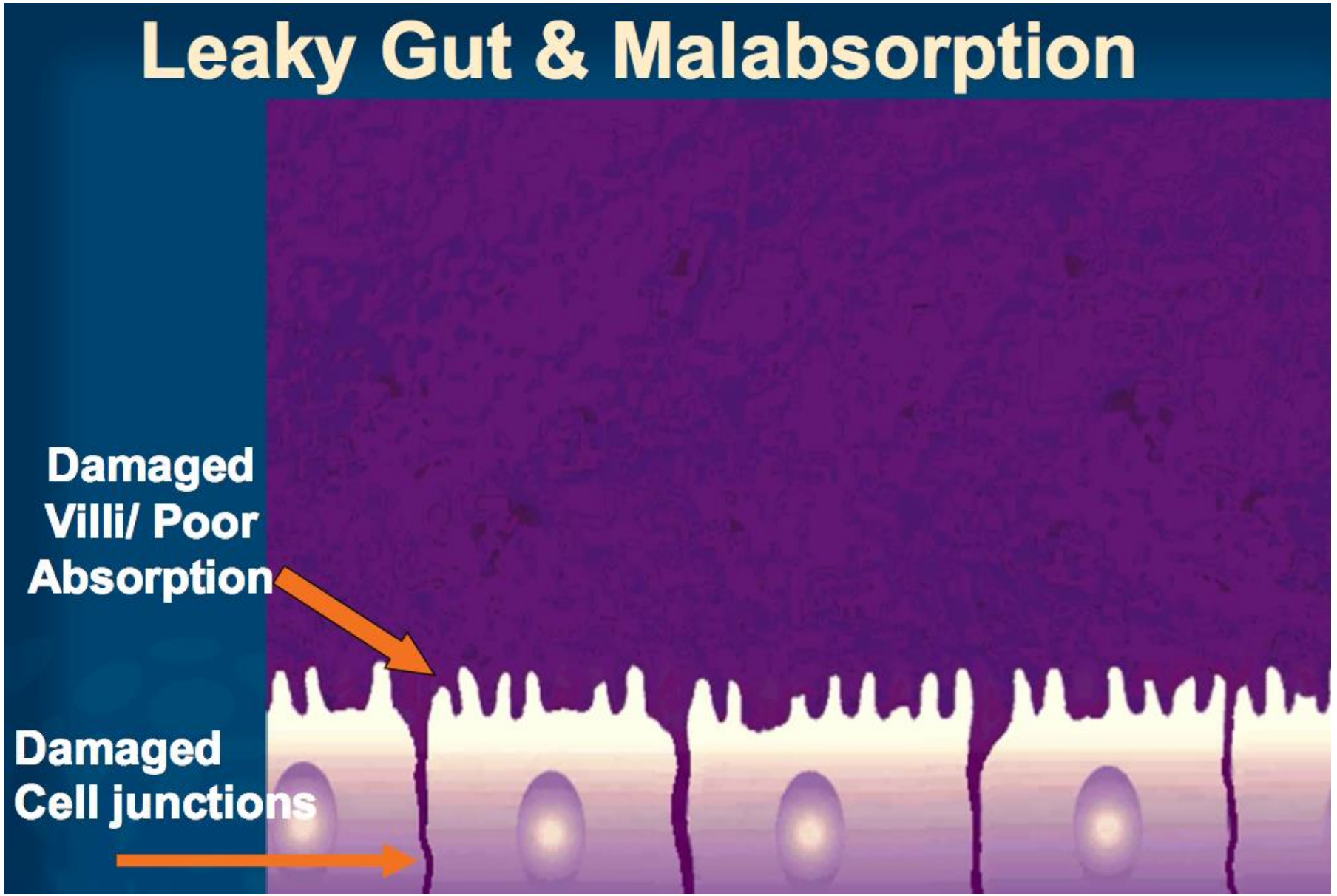









Healthy Gut
Healthy
Villi/Good
Absorption
Healthy Tight
Junctions


Leaky Gut & Malabsorption
Damaged Villi/ Poor Absorption
Damaged Cell junctions

The 7 keys for Functional Medicine

- Optimize nutrition
- Balance hormones
- Reduce inflammation
- Fix digestion
- Enhance detoxification
- Boost energy metabolism
- Calm the mind

The 5R Program

- Remove
- Repair
- Restore
- Reinoculate
- Rebalance

Modify attitude, diet, stress management

“Food is your medicine”
“Kitchen is your pharmacy”
“Lifestyle is your physician” Hippocrates

Heal the Gut

The small intestine renews its lining every 4-7 days!

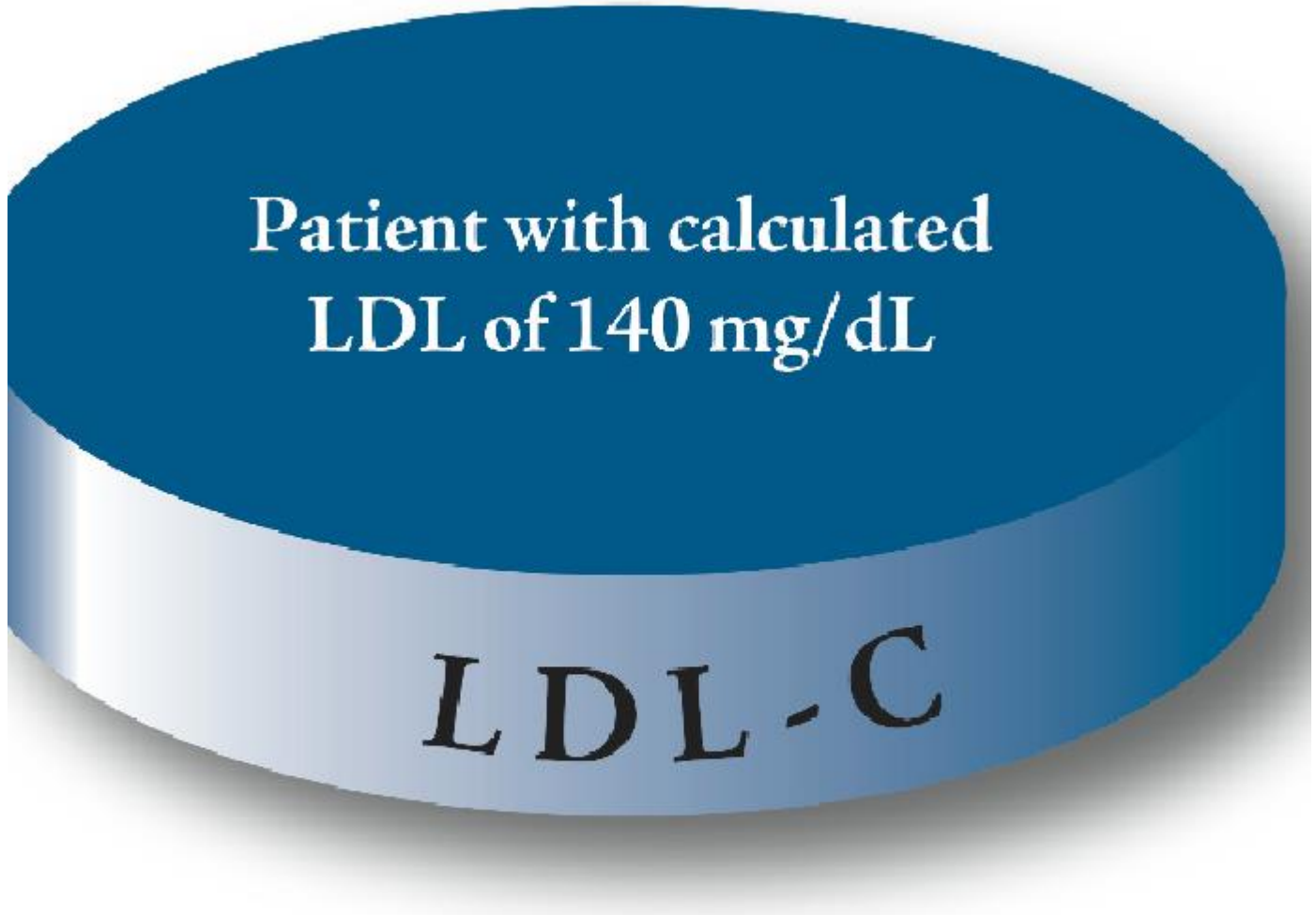
Healing the gut:

– Adequate essential fats

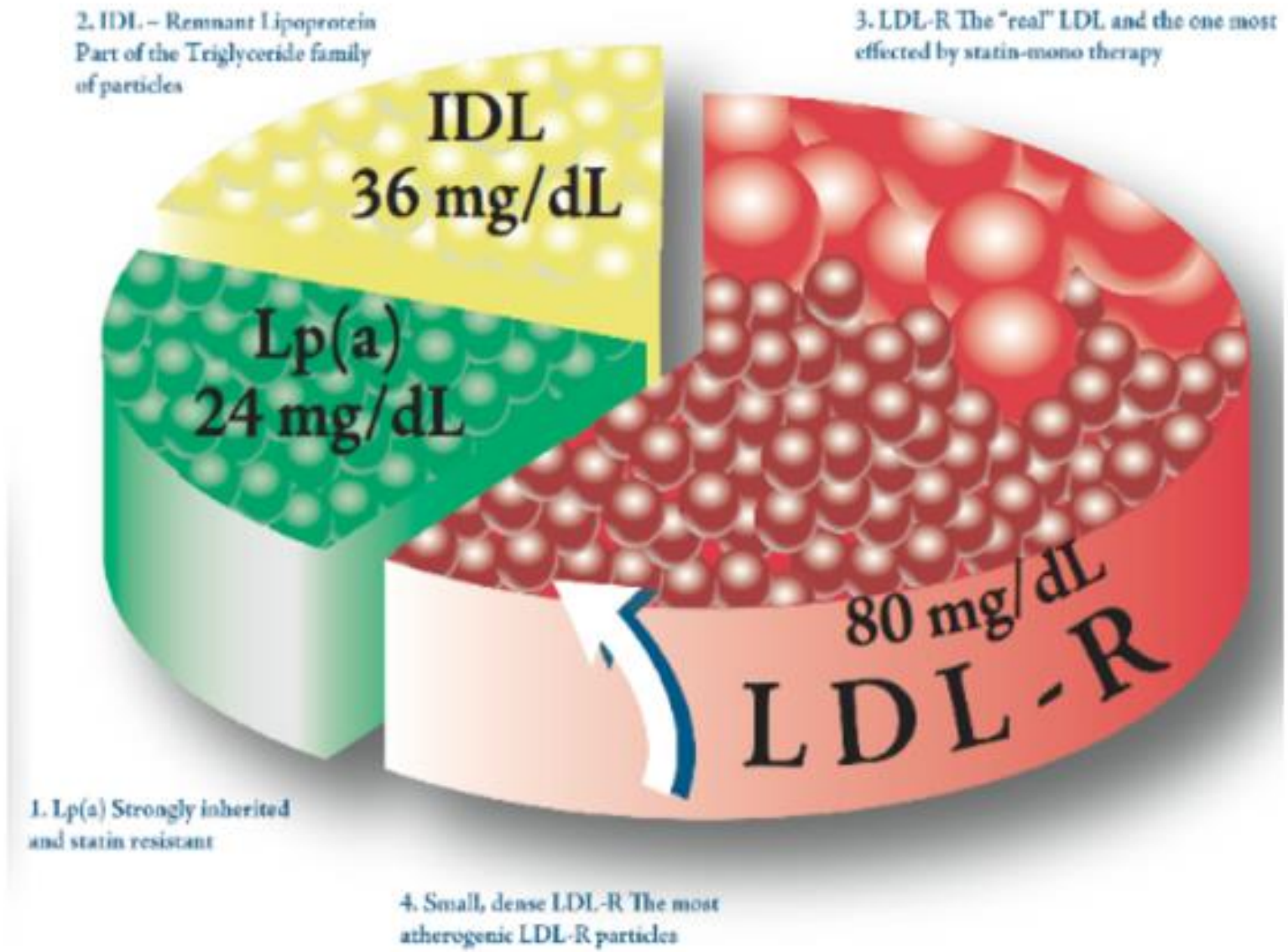
– Adequate glutamine

– Adequate magnesium, probiotics

Test Name	Optimal	Borderline	Increased Risk	Footnotes	Previous Results
Lipid Tests					
Total Cholesterol[1]		**218**		9	
	<200	**200-240**	>240 mg/dL		
Direct LDL-C[1]		**108**		9	
	<100	**100-160**	>160 mg/dL		
HDL-C[1]		**49**		9	
	>50	**40-50**	<40 mg/dL		
Triglycerides[1]		**155**		9	
	<150	**150-200**	>200 mg/dL		
Non-HDL-C		**169**		9	
	<130	**130-190**	>190 mg/dL		
ApoB[1]			**139**	9	
	<80	80-120	**>120 mg/dL**		
Lp(a)[1]		**33**		9	
	<30	**30-50**	>50 mg/dL		
Lipid Ratios					
TC/HDL-C		**4.4**		9	
	<4	**4-6**	>6		
HDL-C/TG		**0.32**		9	
	>0.5	**0.25-0.5**	<0.25		
Inflammation and Oxidation Tests					
hs-CRP[1]			**3.4**	9	
	<1.0	1.0-3.0	**>3.0 mg/L**		
Interpretation: HIGH hs-CRP may indicate inflammation and may be associated with increased CVD risk.					
Consideration: Consider evaluating potential contributing CVD risk factors. Identify and treat underlying causes such as atherogenic lipoproteins. If indicated, control blood pressure, encourage smoking cessation and weight reduction.					
Metabolic Tests					
HbA1c[1]	**5.6**			9	
	<5.7	5.7-6.4	>6.4 %		
Glucose[1] [2]	**98**			9	
	70-99	100-125	<70 or >125 mg/dL		
Interpretation: Based on the HbA1c value, the estimated Average Glucose (eAG) is 114 mg/dL which includes the non-fasting state.					
Homocysteine[1]		**11.5**		9	
	<10.0	**10.0-14.0**	>14.0 µmol/L		



Low to moderate risk when using a calculated LDL.


2. IDL – Remnant Lipoprotein
Part of the Triglyceride family
of particles
3. LDL-R The "real" LDL and the one most
effected by statin-mono therapy
IDL
36 mg/dL
Lp(a)
24 mg/dL
80 mg/dL
LDL-R
1. Lp(a) Strongly inherited
and statin resistant
4. Small, dense LDL-R The most
atherogenic LDL-R particles

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WILEY CLINICAL CARDIOLOGY

CLINICAL INVESTIGATIONS

Consumption of a defined, plant-based diet reduces lipoprotein(a), inflammation, and other atherogenic lipoproteins and particles within 4 weeks

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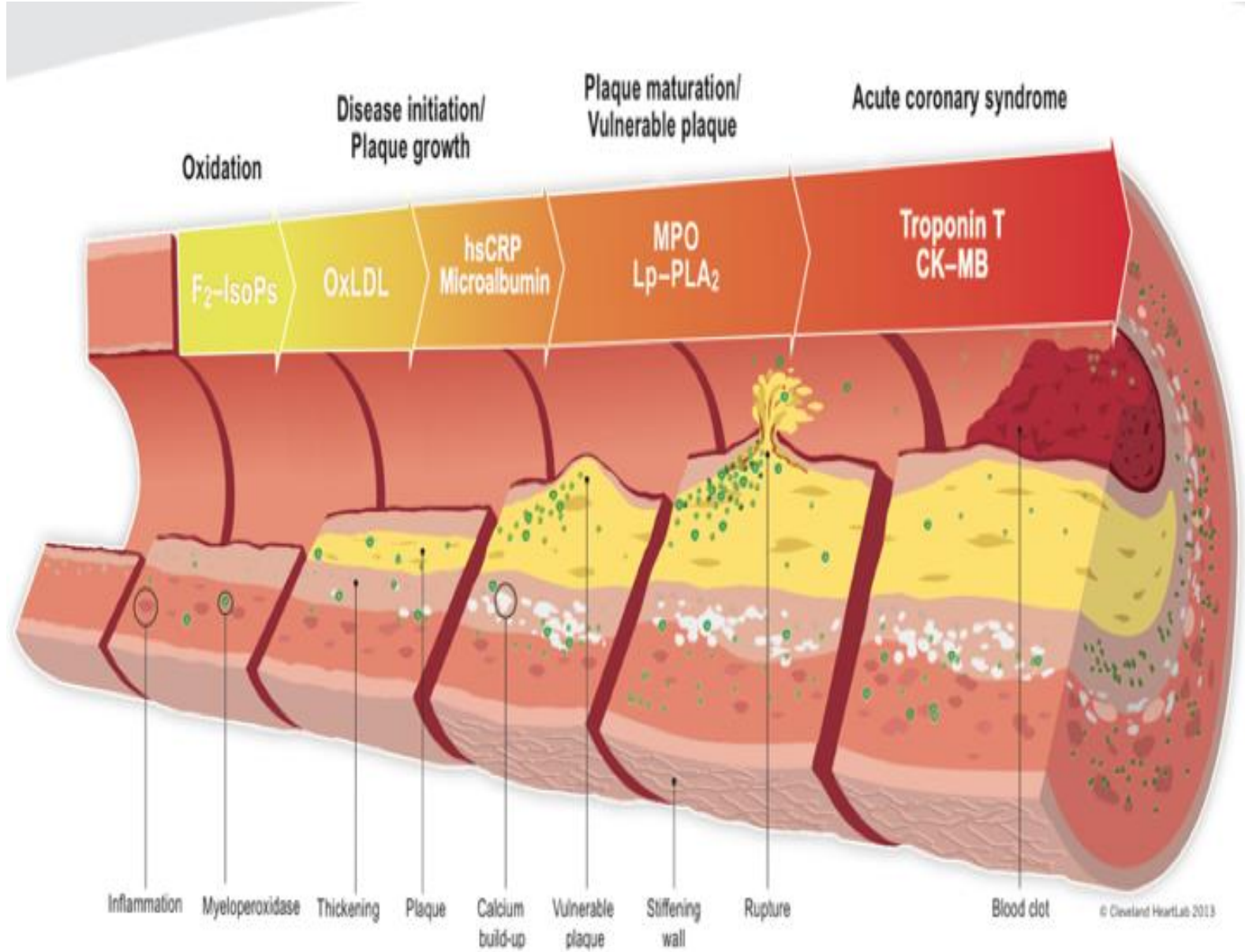
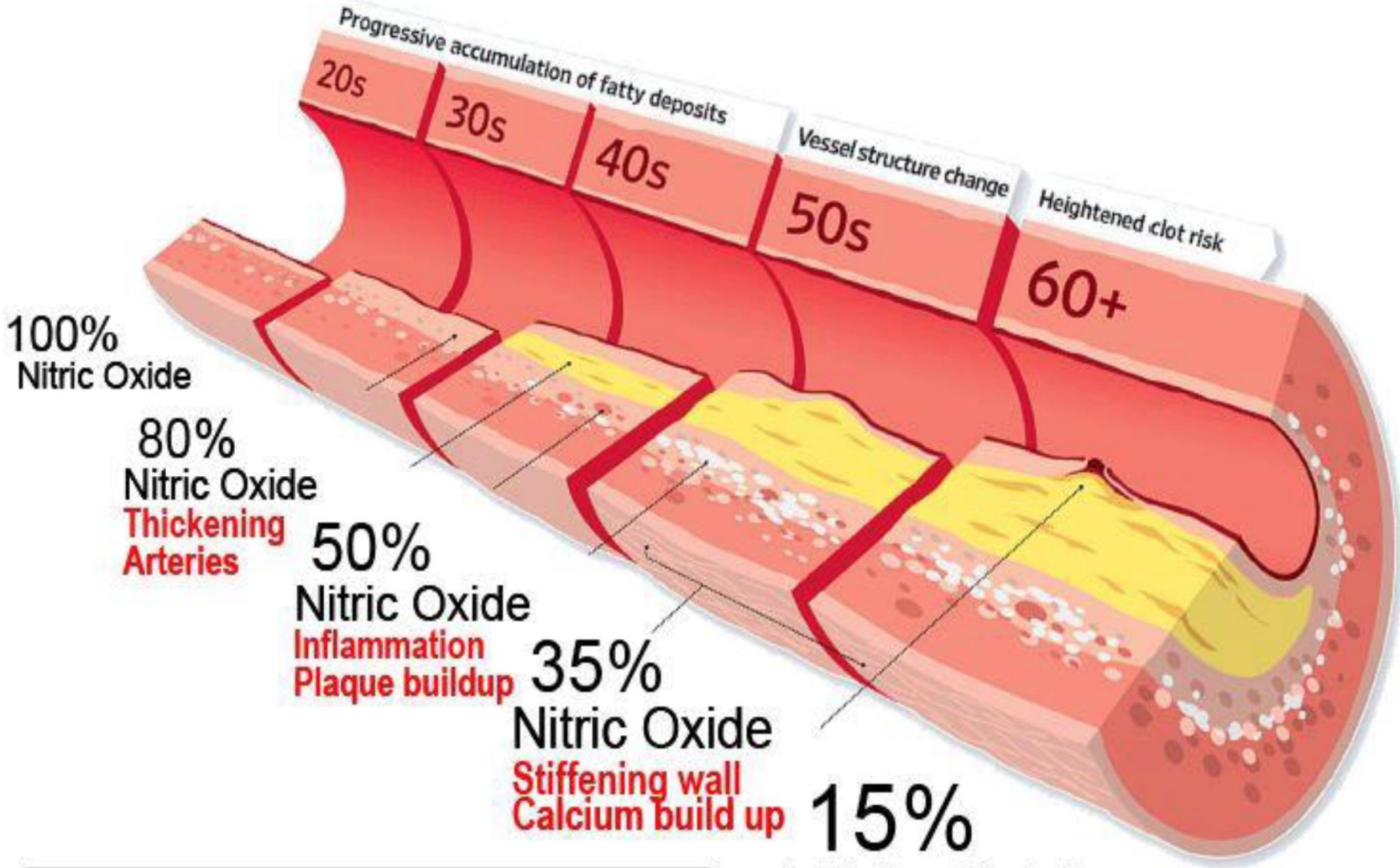
Background: Lipoprotein(a) [Lp(a)] is a highly atherogenic lipoprotein and is minimally effected by lifestyle changes. While some drugs can reduce Lp(a), diet has not consistently shown definitive reduction of this biomarker. The effect of consuming a plant-based diet on serum Lp(a) concentrations have not been previously evaluated.

Hypothesis: Consumption of a defined, plant-based for 4 weeks reduces Lp(a).

Methods: Secondary analysis of a previous trial was conducted, in which overweight and obese individuals (n = 31) with low-density lipoprotein cholesterol concentrations >100 mg/dL consumed a defined, plant-based diet for 4 weeks. Baseline and 4-week labs were collected. Data


Oxidation
Disease initiation/
Plaque growth
Plaque maturation/
Vulnerable plaque
Acute coronary syndrome
F2-IsoPs
OxLDL
hsCRP
Microalbumin
MPO
Lp-PLA2
Troponin T
CK-MB
Inflammation
Myeloperoxidase
Thickening
Plaque
Calcium
build-up
Vulnerable
plaque
Stiffening
wall
Rupture
Blood clot
© Cleveland HeartLab 2013



As we age, we lose 85% of our ability to make Nitric Oxide.

Based on average males
Compilation of data from multiple published reports in humans
Gerhardt et al Hypertension 1996
Celermajer et al JACC 1994
Taddei et al Hypertension 2001
Egashira et al Circulation 1993

In your 60's and beyond, the aging process partly reflecting the arteries withstanding more than **100,000** heart beats a day, contributes to the attack on the lining of the arteries. Meantime, left ineffectively checked, plaques can rupture or erode, leading to blood clots that can cause heart attacks, while an overworked or scarred heart

Did it Work?

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Do Cholesterol Drugs Do Any Good?

Research suggests that, except among high-risk heart patients, the benefits of statins such as Lipitor are overstated

by John Carey

Martin Winn's cholesterol level was inching up. Cycling up hills, he felt chest pain that might have been angina. So he

THIS ISSUE

January 28, 2008
Lipitor

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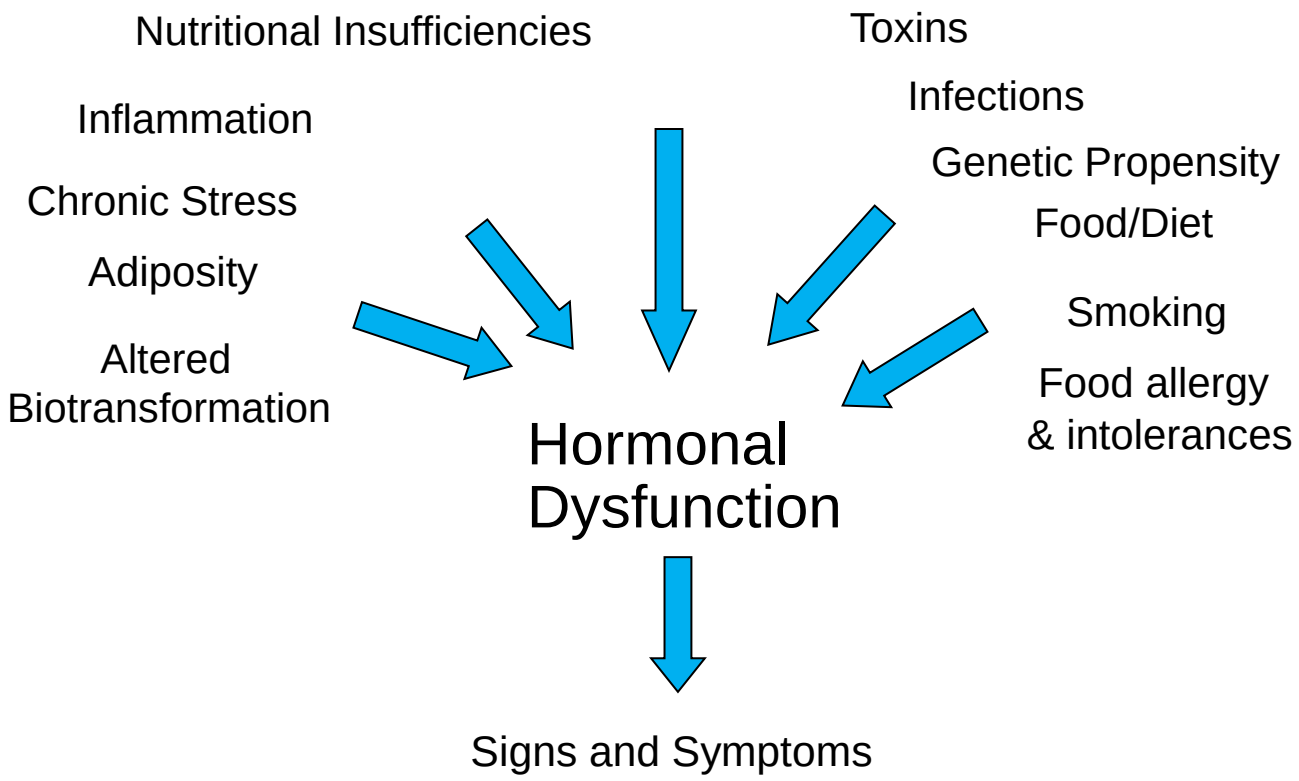
Close
Record EKG
Great Signal
24
70 BPM
How are you feeling?
For example, say "Dizzy".
Kardia


Eko

What Disrupts Hormonal Balance?



Pituitary, Thyroid, Adrenal, **Hormone**

Balance the Symphony!

Pituitary-at the base of the brain

Thyroid-butterfly shaped organ in the neck

Adrenals-walnut sized organs on top of each kidney

Ovaries

The Magic of Food

Bioenergetics of the Beating Heart

- Humans produce and consume their body weight in ATP daily (65 kg)
- **Heart accounts for approximately 0.5% of body weight, yet uses roughly 8% of ATP**
- **Heart stores enough energy to pump for only a few beats**
- Heart contains highest concentration of mitochondria of all tissues
- 90% of cellular ATP is utilized to support contraction-relaxation of myocardium

Thank you for Attending