

Hyper-insulinemia, Insulin Resistance and the Optometrist

A multipronged Public Health &
OD Practice Enhancing Initiative

2 April 2017 1-4 PM

ONS / UMSSL X

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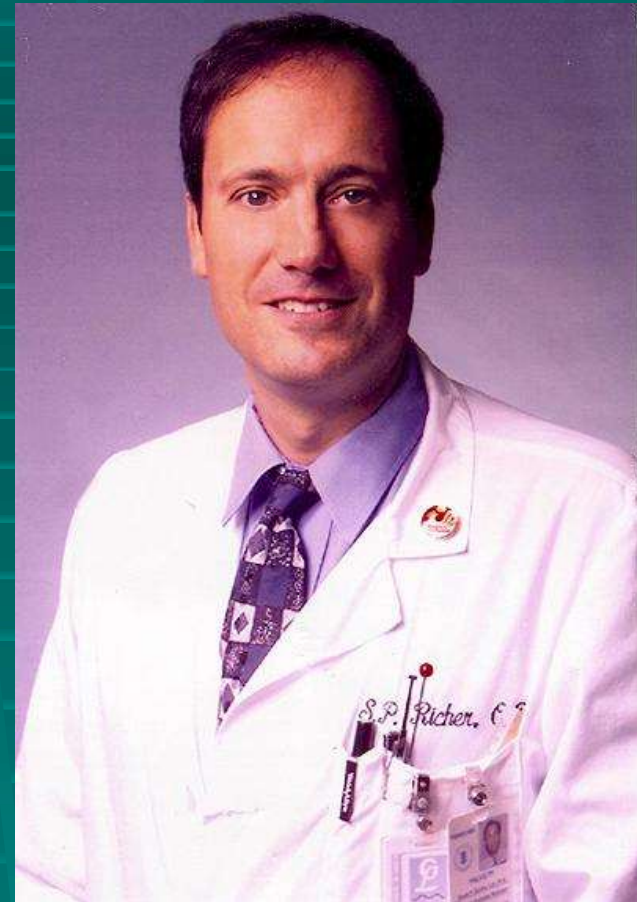
Disclosures – none

Research Grants

Kemin Health – LAST study
Chrysantis – ZVF study
IL Society Prevent Blindness
Longevinex ® Associates
ZeaVision (Night Vision)

Consultant

Bausch + Lomb
Nestle Purina
Essilor / Stereo Optical Inc
Annidis Health Systems
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www.ContactLensAndVision.com

Kerry Gelb, OD President, ALLDOCS

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State of New Jersey
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BATCH # PRT120224A44754 DEA # SERIAL # 0000003

IF PRESCRIPTION IS WRITTEN AT ALTERNATE PRACTICE SITE, CHECK HERE
AND PRINT ALTERNATE ADDRESS AND TELEPHONE NUMBER ON REVERSE SIDE

PATIENT _____ D.O.B. _____
ADDRESS _____ DATE _____

Rx NOT VALID FOR SCHEDULE II CONTROLLED DANGEROUS SUBSTANCES.

Reminder:
12-Hour Fasting Time

CBC	Ferritin
CMP	Thyroid Panel + Reverse T3
HbA1c	Fibrinogen
25 Hydroxy Vitamin D	NMR Lipid Profile
Fasting Insulin	Oxidized LDL
2-Hour Insulin Levels	LP (a)
2-Hour GTT	ApoA
hs-CRP	ApoB
Homocysteine	(sigA) Anti-Gliadin Antibody Test
Uric Acid	Other _____

DX Code: 362.81 790.6 V58.69 366.16 371.41 368.80
Retinal Abnormal High Risk Cataracts Corneal Blurry Other
Hemorrhage Blood Tests Medicine Arcus Vision

DO NOT REFRIL _____ SIGNATURE OF PRESCRIBER _____
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Use separate form for each controlled substance prescription
THEFT, UNAUTHORIZED POSSESSION AND/OR USE OF THIS FORM INCLUDING ALTERATION OR FORGERY, ARE CRIMES PUNISHABLE BY LAW



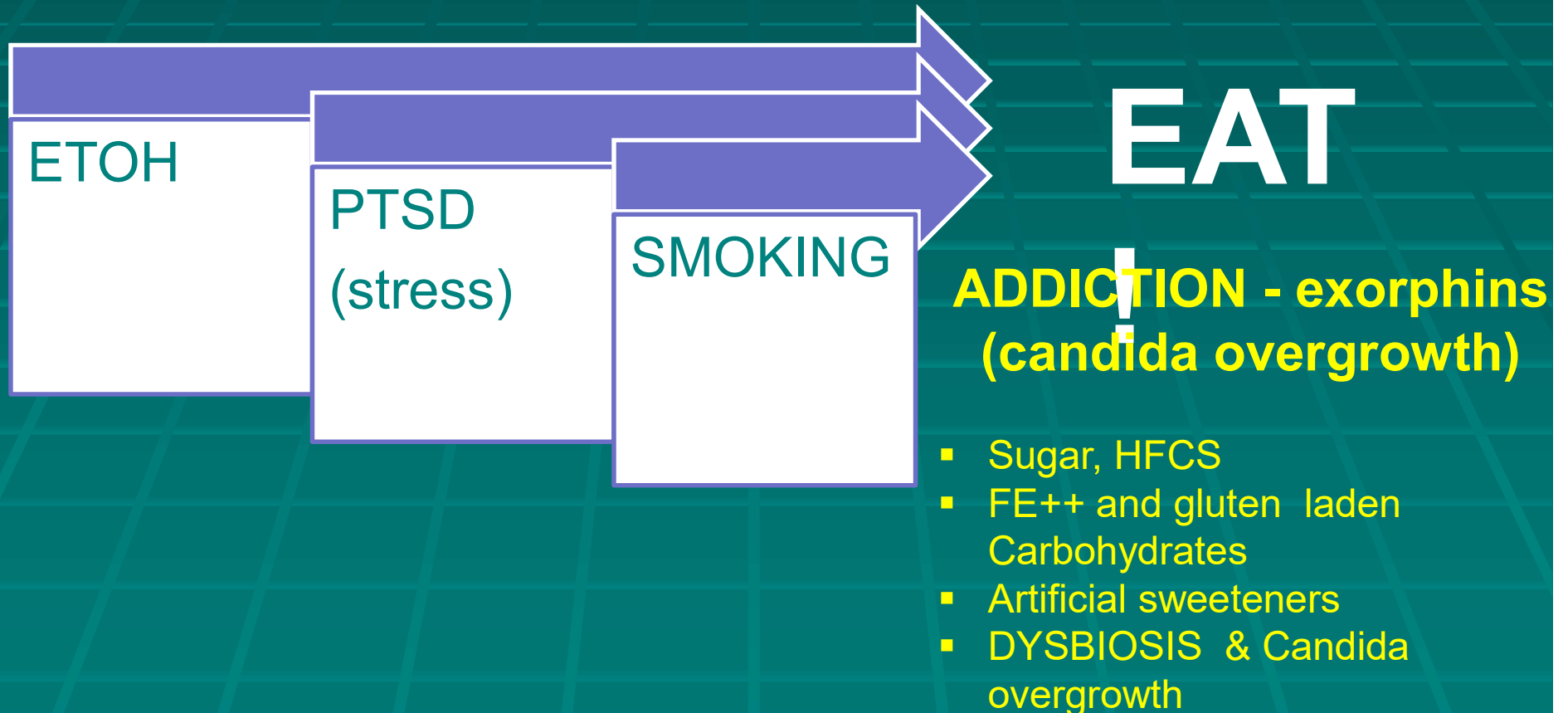
New ONS Board Member

– every 3rd veteran at our medical center has diabetes

Summary

- **USDA Food Triangles have been a monumental failure**
- **It isn't fat and cholesterol**
- **It isn't willpower**
- **It isn't more exercise & health clubs**
- **And it isn't Obesity or BMI**

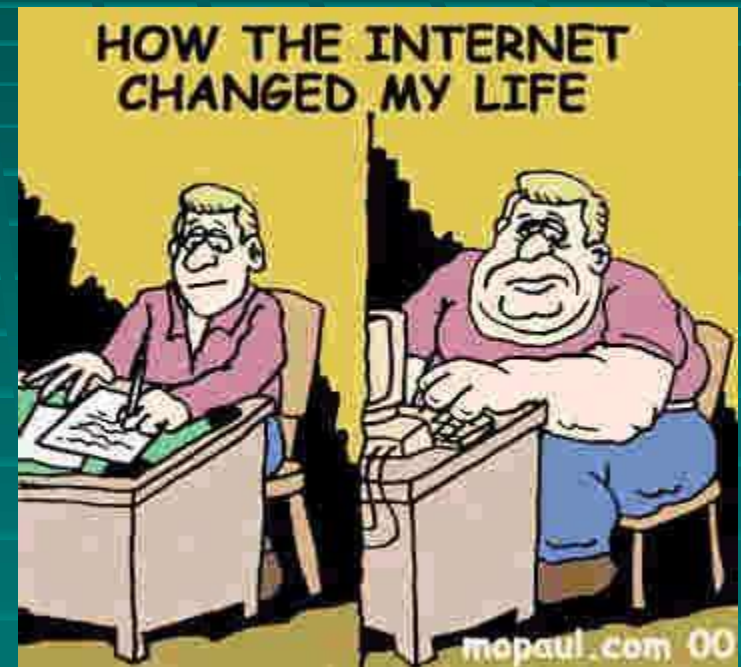
Veteran Diabetes Epidemic (often ETOH + SUGAR)



Diabetes (Type II) -95 %

(↑ *poor quality food* and ↓ *activity and other behaviors*)

Has increased in incidence between 600 and 1000% in the last 60 years. Every year, 6.5 % more people have the disease than the year before.



An epidemic

Lecture Objectives

- Why is diabetes skyrocketing out of control?
- Define and understand **Hyper-insulinemia** and **Insulin Resistance (IR)** as the universal foundation of poor health.
- Learn how to decrease hyperinsulinemia
- Learn how to detect insulin resistance (IR)
 - promote insulin sensitivity
- The Proactive Optometrist

Poor Medicine vs. Great Medicine

AGING & CHRONIC DISEASE CHRONIC DEGENERATION

- Day to Day Living
 - MDs, PAs, NPs = “Middle Men”
- “Primary Care” - AKA
 - “Evidence Based “Medicine
 - Pharmaceutical Medicine
 - Statistical Medicine
 - Outcome Measure Medicine
 - Lab test End point Medicine
- Problematic Specialties
 - Oncology
 - Psychiatry
 - Cardiology
 - Pediatrics

HEROIC MEDICINE

- Trauma, ER
- Pain
- Infections (serious)
- Transplant surgery
- Orthopedics
- Neurosurgery
- Ophthalmology

The nature of the change from a “Pill for an Ill” to treating the cause

COMMENTARY

The Conflict Between Complex Systems and Reductionism

Betsy H. Q. Hoag, PhD

DENIGMATICLY BEING TYPICALLY POSSIBLE HAS HAD A PROFOUND influence on medicine. Striving to explain a clock as which each broken part is fixed to order, investigators have attempted to discover causal relationships among key components of an individual and to treat those components accordingly. For example, if most of the morbidity in patients with diabetes is caused by high blood glucose levels, this control of those levels should relieve the system to normal and the patient's health problems should disappear. However, in one recent study, the strategy of more intensive glucose control resulted in increased risk of death.¹ Likewise, chemotherapy often actually reduces tumor size but also produces severe adverse effects leading to other complications, including the progression of secondary tumors. Most important, little evidence exists that more aggressive chemotherapy prolongs life for many patients.^{2,3} In fact, chemotherapy may have overall negative effects for some patients.

Most medical treatments make claims based on research of specific molecular pathways, so why do unexpected consequences occur after years of treatment? More simply, does the treatment that addresses a specific disease-related component harm the individual as a whole?

To address these questions, the conflict between reductionism and complex systems must be analyzed. With increasing technological capabilities, these systems can be examined in increasingly smaller components, from organ to cells to chromosomes, and from classifications to genes. Paradoxically, the success of science also leads to blind spots in thinking as scientists become increasingly reductionist and deterministic. The expectation is that as the resolution of the analysis increases, so too will the quantity and quality of information. High-resolution studies focusing on the building blocks of a biological system provide specific insights on which molecular errors can be fixed.

While the DNA sequence of the human genome is known, the functions of these genes are not understood in the context of a dynamic network and the resultant bioinformatic relationships to human dynamics. Mutations in many genes are known to contribute to cancers in experimental systems, but the common mutations that actually cause cancer cannot yet be determined.⁴

Many therapies such as antibiotics, painkillers, blood transfusions, and organ transplantation have worked well using classic approaches. In these cases, interventions were successful in treating a specific part of a complex system without triggering system chaos in many patients. However, even

for these relatively safe interventions, unpredictable risk factors still exist. For every intervention that works well there are many others that do not, most of which involve complicated pathways and multiple levels of interaction. Even apparent major successes of the past have developed problems, such as the emergence and potential spread of super pathogens resistant to available antibiotic arrays.

One common feature of a complex system is its emergent properties—the collective results of distinct and interactive properties generated by the interaction of individual components. When parts change, the behavior of a system can sometimes be predictable—but often cannot be if the system exists on the “edge of chaos.” For example, a disconnect exists between the status of the parts (such as tumor response) and the system behavior (such as overall survival of the patient). Furthermore, nonlinear responses of a complex system can undergo sudden, massive and stochastic changes in response to what may seem to be minor perturbations. This can occur despite the same system displaying regular and predictable behavior under other conditions.^{5,6} For example, patients can be harmed by an immunomodulatory effect of a commonly used nutrient when the system displays chaotic behavior under common conditions. This stochastic effect is what causes sepsis. Given that any medical intervention is a stressor to the system and that multiple system levels can respond differently, researchers must consider the systemic response of the entire human system to drug therapy rather than focusing solely on the targeted organ or cell or on one particular molecular pathway or specific gene. The same approach is necessary for monitoring the clinical safety of aging.

Other challenging questions arise as considerations. Once an entire system enters the disease progression, how should the system be restored following replacement of a defective part? If a system is altered, should it be brought back to the previous status, or is there a new standard defining a more stable system? The development of many diseases can take years, during which time the system has adapted to function in the altered environment. These changes are not restricted to a few clinically recognized factors that can provide the whole system, which may have adapted to new interactions with new dynamic interactions, functioning with a few factors without considering the entire system can often result in further stress to the system, which might trigger a decline in system chaos. For many disease conditions resulting from years of adaptation, gradual

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- Medical therapeutics evolved as a single agent to treat a single biological endpoint (i.e. reductionism).
- **Current understanding of the cause of chronic diseases is that there is no “one cause” for any disease, so need multiple safe “shots on goal” (i.e. complex systems approach seen in personalized lifestyle medicine)**

J Am Med Assoc 2008;1580-81.

IR / Diabetes

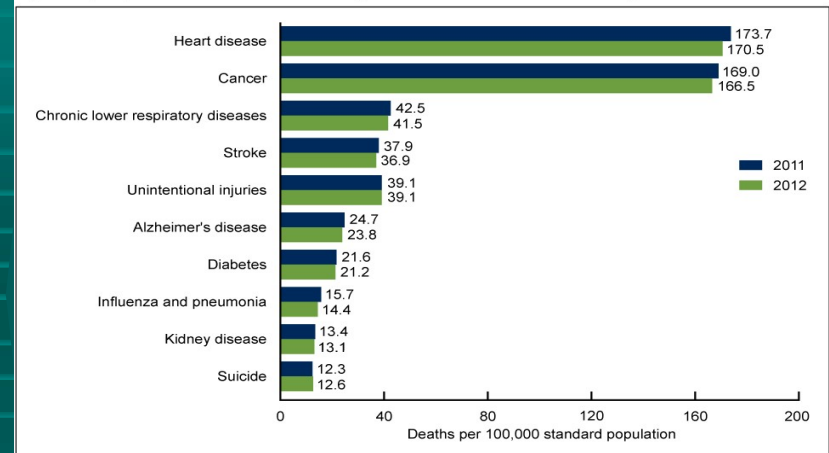
- 1 billion world wide
- > 100 million Americans
- Most common cause of chronic disease
 - CVA, CVD, CA, dementia, kidney, blindness
- The single biggest contributor to our health care costs and our national debt.
- 70% percent of our federal budget is spent on Medicaid, Medicare and Social Security. It is unsustainable.
- Current approach not working
 - Because treating symptoms not cause



Diabetes Mellitus

1. Type 2 DM (NIDDM)
2. Not merely “ SUGAR DISORDER”
3. Multi system disease – A syndrome
4. Metabolic – endocrine – vascular
5. Cardiac – cerebral – renal – ophthalmic

Figure 3. Age-adjusted death rates for the 10 leading causes of death in 2012: United States, 2011–2012



NOTE: Access data table for Figure 3 at: http://www.cdc.gov/nchs/data/databriefs/db168_table.pdf#1.
SOURCE: CDC/NCHS, National Vital Statistics System, Mortality.

Diabetes is a National Health Epidemic

Obesity is up 30% past 10 years



- 2/3 of us are overweight or obese
- 33% of Americans obese VS 1950 when only 3.5% were obese.
 - More than Double from the early 60's
- **Straight-line connection between BMI and death, but**
- **% body fat, NAFLD and waist / height ratio better associated with IR**

“The OD is the New GP”

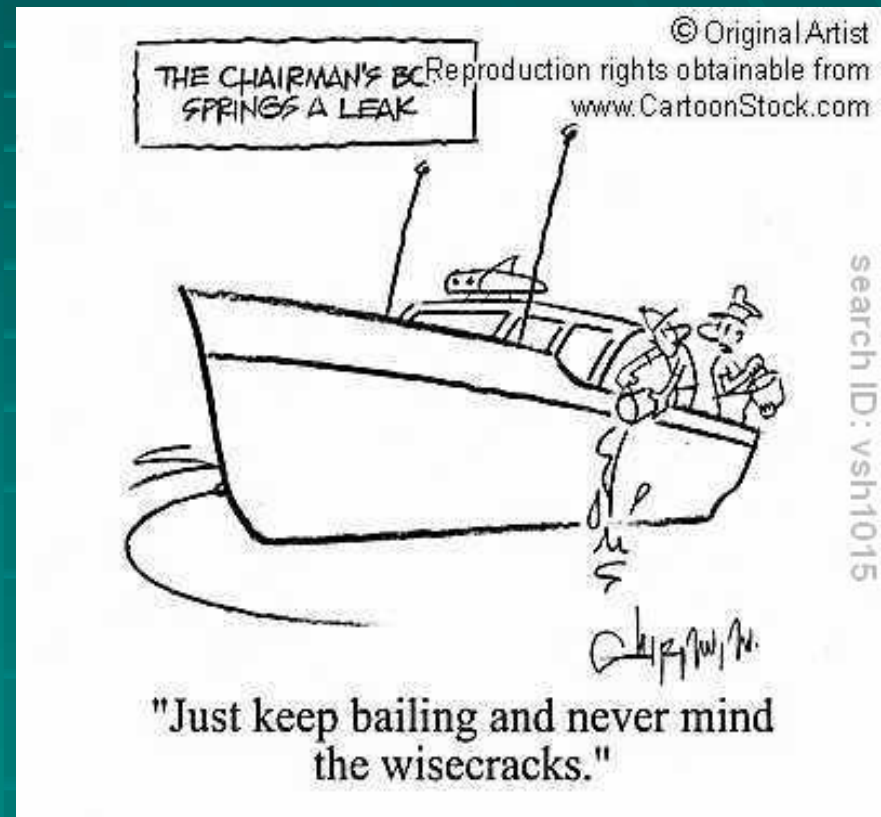
Dr. Renzi

- We examine 110 million Americans every year
- We examine Americans every 2.6 years
 - Refractive changes
 - Ocular health changes
- The eyes are a biomarker of aging
 - Direct view of blood vessels
 - Direct view and functioning of neural tissue
 - Successful aging vs. Non-successful aging apparent
- The eyes are a biomarker of brain health
 - Become a Health Coach (**Doctor as Teacher**)
 - Stress general USDA guidelines / recommendations

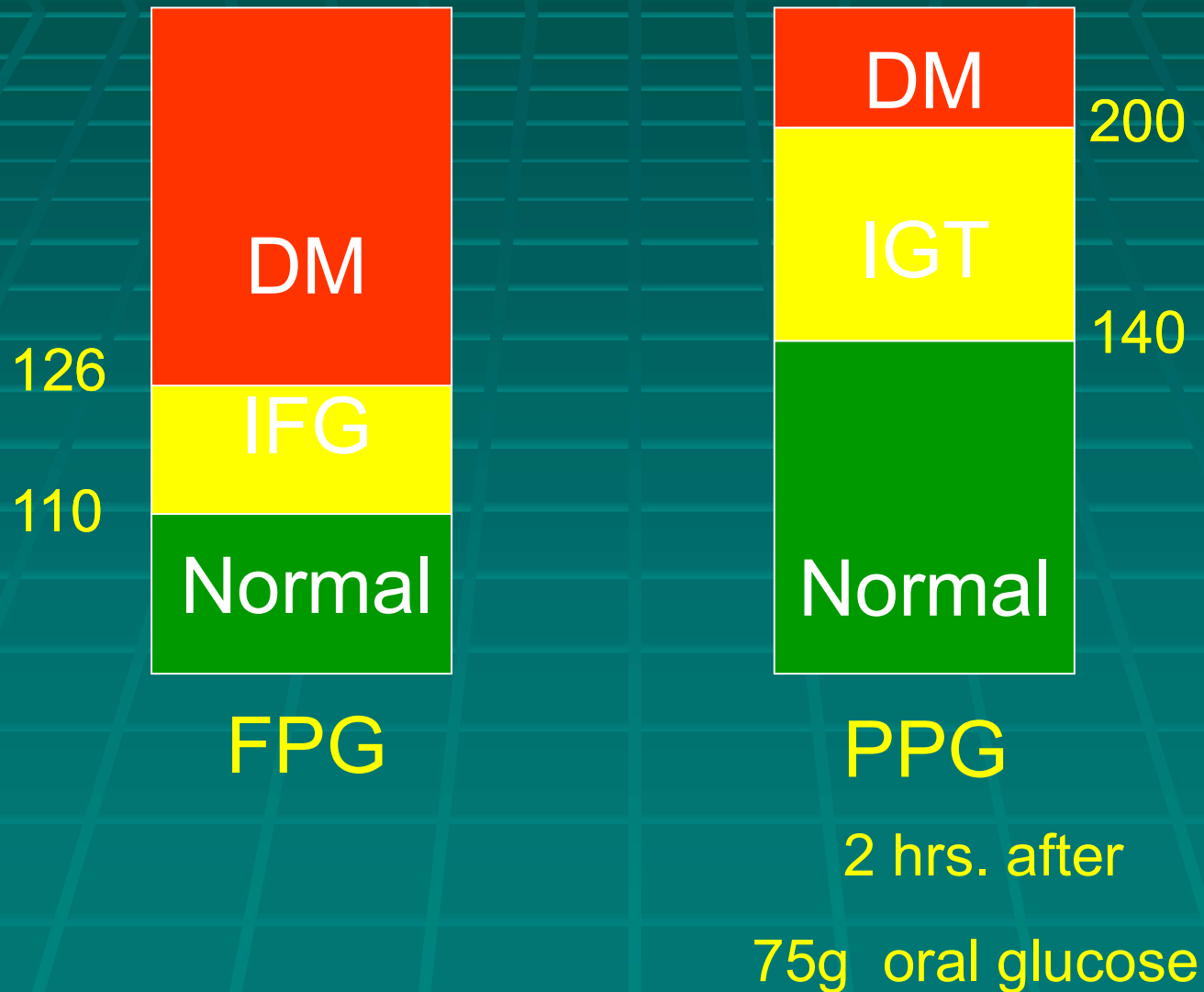
US Medicine 2017

Treating Symptoms (not root cause)

Elevated BS, BP, lipids are downstream
suffering symptoms of a Poor Lifestyle



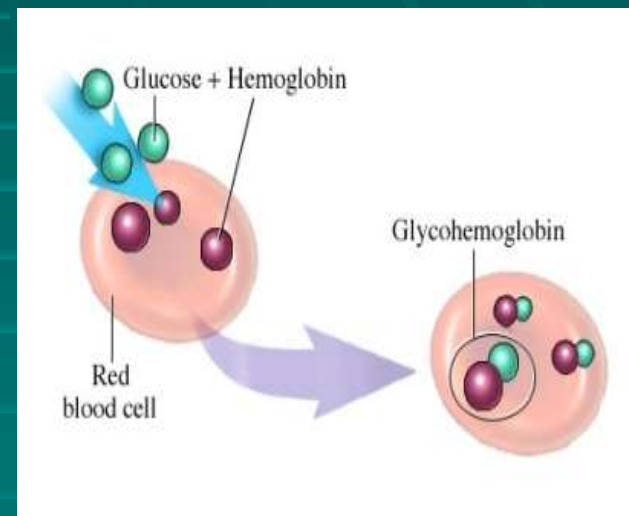
Diagnosis – FBG and GTT



HbA1c

a measure of cell damage

- Glycosylated hemoglobin – average plasma glucose levels over a 3 month period
- % of Glucose that sticks to hemoglobin
- Therefore, the more glucose in blood the greater the A1C
- RBC's last about 3 months
- **Normal is 4%-"5.6%"**
- **But an A1C of 5% to 6% increases MI risk by 3x**



A1c-derived average glucose (ADAG)

A1C in average BS

- Example A1C of 6.7%=146mg/dl
- Average Plasma Blood Glucose A1C Result
- 5% = 100 mg/dL

Average* Dally Blood Sugar	A1c Level
135	6%
170	7%
205	8%
240	9%
275	10%
310	11%
345	12%

* Average is based on readings taken before and after meals, and at bedtime.

Diagnosis of type 2 Diabetes (international consensus statement)

- Diagnosis of Diabetes HbA1c \geq 6.5
 - Fasting plasma glucose (FPG) \geq 126mg/dl on 2 occasions
 - Random plasma glucose $>$ 200mg/dl on 2 occasions with symptoms (polydipsia, polyuria or unexplained weight loss)
 - Oral glucose tolerance test (OGTT) $>$ 200mg/dl at 2 hours

Conventional Treatment Strategy

Defect in insulin sensitivity

1. “Exercise” – aerobic, consistent
2. “Weight reduction – Diet, drugs”
3. Metformin
4. Glitazones- Thiazolidinediones

Defect in insulin secretion

1. Pancreatic β cell stimulation - SU,
Repaglinide
2. Insulin exogenous supplementation

Conventional Treatment Strategy

Curb Increased hepatic glucose output

1. Metformin better than Glitazones
2. Insulin Supplementation

Decrease Carbohydrate absorption

(post-prandial hyperglycemia)

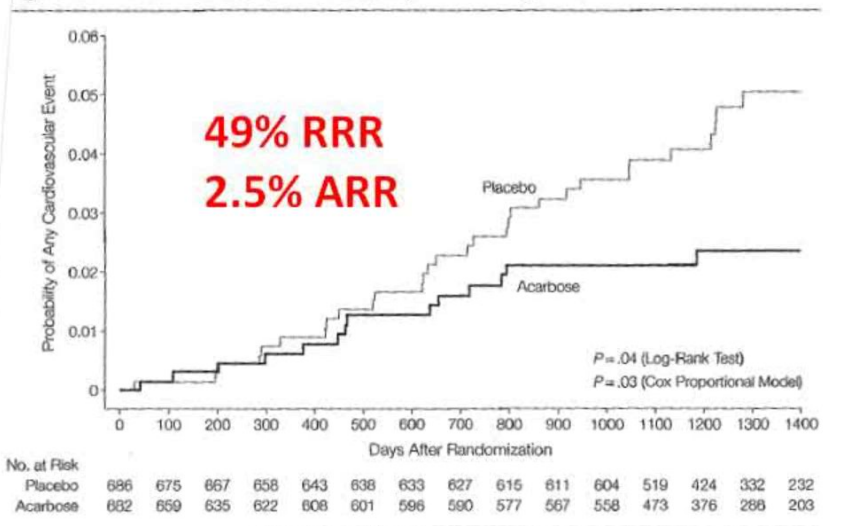
1. Acarbose (Precose[®])

Often the defects are multiple and hence the need for combination of the above strategies

Acarbose Decreases Risk of CVD and HTN

Lowering glucose without raising insulin improves outcomes

Figure 2. Effect of Acarbose on the Probability of Remaining Free of Cardiovascular Disease



Randomized
1,429
patients
3.3 year
follow up

Acarbose Treatment and the Risk of Cardiovascular Disease and Hypertension in Patients with Impaired Glucose Tolerance

JAMA 2003; 290: 486-494

DM Drug Treatment



Metformin– glucophage - IR+

Can cause B12 deficiency and peripheral neuropathy often misdiagnosed diabetic neuropathy and can increase homocysteine, S/E depression and fatigue, B supplements recommended
reduces **free testosterone** and **total testosterone**

TZD- thiozolidinidione ACTOS / AVANDIA - IR

High insulin effect
S/E weight gain, CHF, MI, Cancer but decrease A1C
Link between Insulin, Cancer and CVD

Sulfonylurea –glyburide, glipizide, glimepiride, glucotrol – insulin secretagogue

Increase Mortality, morbidity CMAJ 2006
30%-50% increase in CV events compared to metformin..40%-60 risk of death from MI vs Metformin
Cause increased atherosclerosis and CV disease
36% increase cancer vs. Metformin

DPP4/ Incretins Januvia,,Byetta – helps body release insulin, avoiding weight gain

SGLT2 Inhibitors (sodium-glucose cotransporter-2) : A New Class of Diabetes Medications

Inhibitors block the reabsorption of glucose in the kidney, increase glucose excretion, and lower blood glucose levels.

Invokana , Forxiga, Jardiance (Empagliflozin)

S/E Hyperkalemia (Abnormal heart rhythm -- arrhythmia -- that can be life-threatening Slow heart rate)

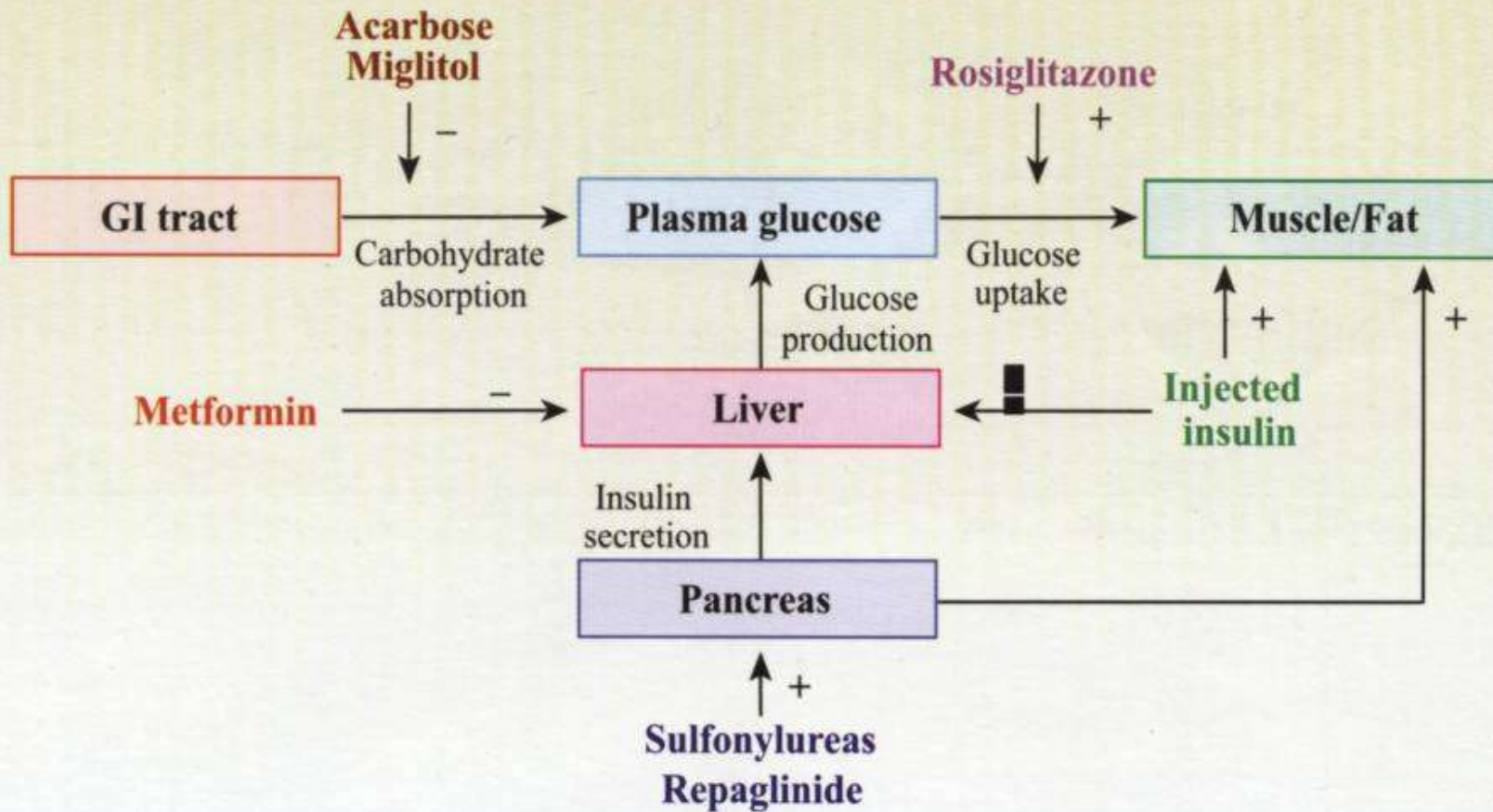
Bone fractures

Insulin

promotes macrophage foam cell formation -----S/E atherosclerosis.

Antihyperglycemic Agents:

Major Sites of Action



Lowering Blood Sugar



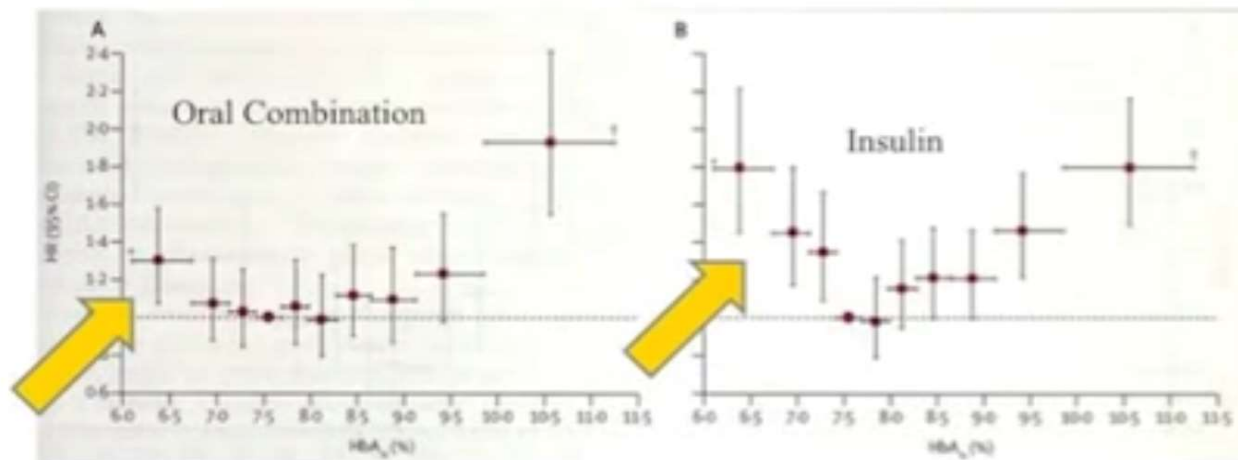
“Lowering your blood sugar without addressing the underlying cause gives you a false sense of security and leads you to believe you are doing something good to prevent heart attacks and early death. Unfortunately the evidence shows otherwise”



Dr Alex Vasquez DC ND DO FACN,

Study 1

Low A1C is **NOT** good for you



Adjusted Hazard Ratios by A1c

27,965 patients intensified from oral monotherapy to combination therapy

Survival as a function of HbA1c in people with type 2 diabetes: a retrospective cohort study

Lancet 2010; 375:481-89. Currie CJ

Study 2

Low A1C is a risk factor

Table 2—Conditional logistic regression model of cardiovascular events

Covariate	Odds ratio (95% CI)	P
Mean A1C level (%)		
≤6.0	1.20* (1.10–1.31)	<0.001
>6.0–8.0	Reference	—
>8.0	1.16* (1.09–1.25)	<0.001
≥6 A1C tests over prior 3 years	0.84 (0.80–0.89)	<0.001
A1C range >1.0%	1.29 (1.21–1.38)	<0.001
Diabetes medications		
Insulin only	2.65 (2.31–3.05)	<0.001
Metformin only	1.06 (0.92–1.23)	0.41
Sulfonylurea only	1.55 (1.36–1.76)	<0.001
Insulin and oral medications	2.56 (2.19–3.00)	<0.001
Other oral medications/oral combination	1.55 (1.33–1.80)	<0.001
No diabetes medications	Reference	—

A1C and Cardiovascular Outcomes in Type 2 Diabetes

Diabetes Care 34:77–83, 2011, Colacayo et al

Nested case control study of 11,157 cases of DM2

ACCORD Trial (Action to Control Cardiovascular Risk in Diabetics)

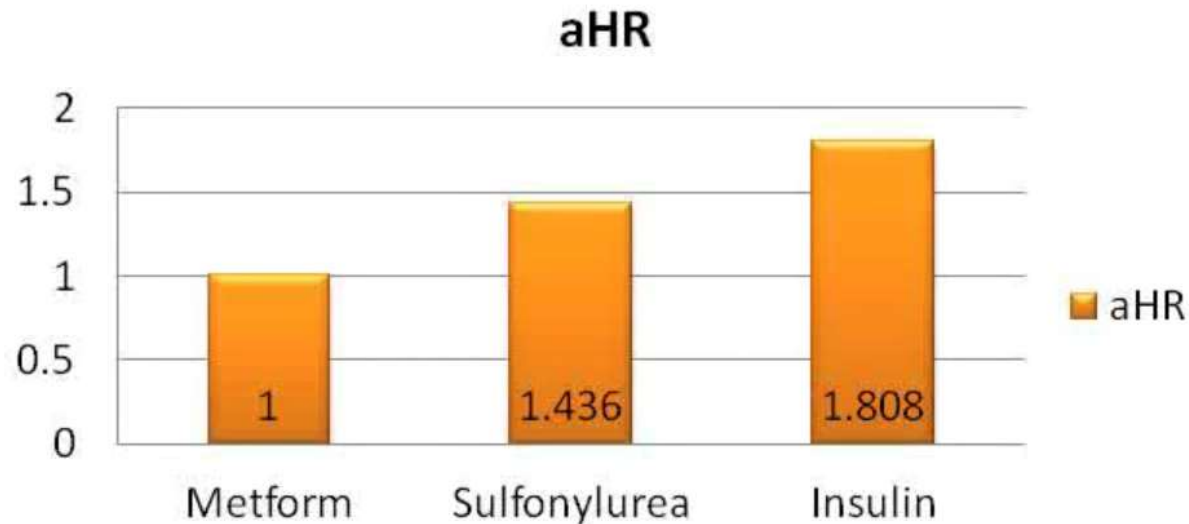
Last updated: November 12, 2014

- As compared with standard therapy, the use of intensive therapy to target normal glycated hemoglobin levels
- Study D/C after 3.5 years
- Increased mortality (approx 20%)
 - Did not significantly reduce major cardiovascular events
 - 27% (gained approximately 10 kg) of weight

Insulin treatment has toxicity

Parameter	Primary End Point			P Value
	aHR	95% CI		
Metformin monotherapy (referent)	1.000			
Sulfonylurea monotherapy	1.436	1.354	1.523	<.0001
Metformin + sulfonylurea	1.024	0.963	1.090	.4454
Insulin monotherapy	1.808	1.630	2.005	<.0001
Insulin + metformin	1.309	1.150	1.491	<.0001

84,622
incident
Type 2
DM cases



Mortality and Other Important Diabetes-Related Outcomes With Insulin vs Other Antihyperglycemic Therapies in Type 2 Diabetes
 J Clin Endocrinol Metab 98: 668–677. 2013 Currie CJ

Side Effects of Treating Type 2 diabetes with Insulin

J Clin Endocrinol Metab. 2013

- *Doubled risk of all-cause mortality*
 - *Twice as many myocardial infarctions*
 - *1.4 time more strokes*
 - *2.1 time more neuropathy*
 - *1.4 times more cancer*
 - *Insulin is a growth factor*
 - *1.7 time more major adverse cardiac events*
 - *3.5 times more renal complications*
 - *1.2 times more eye complications*
 - *2.2 times more deaths*



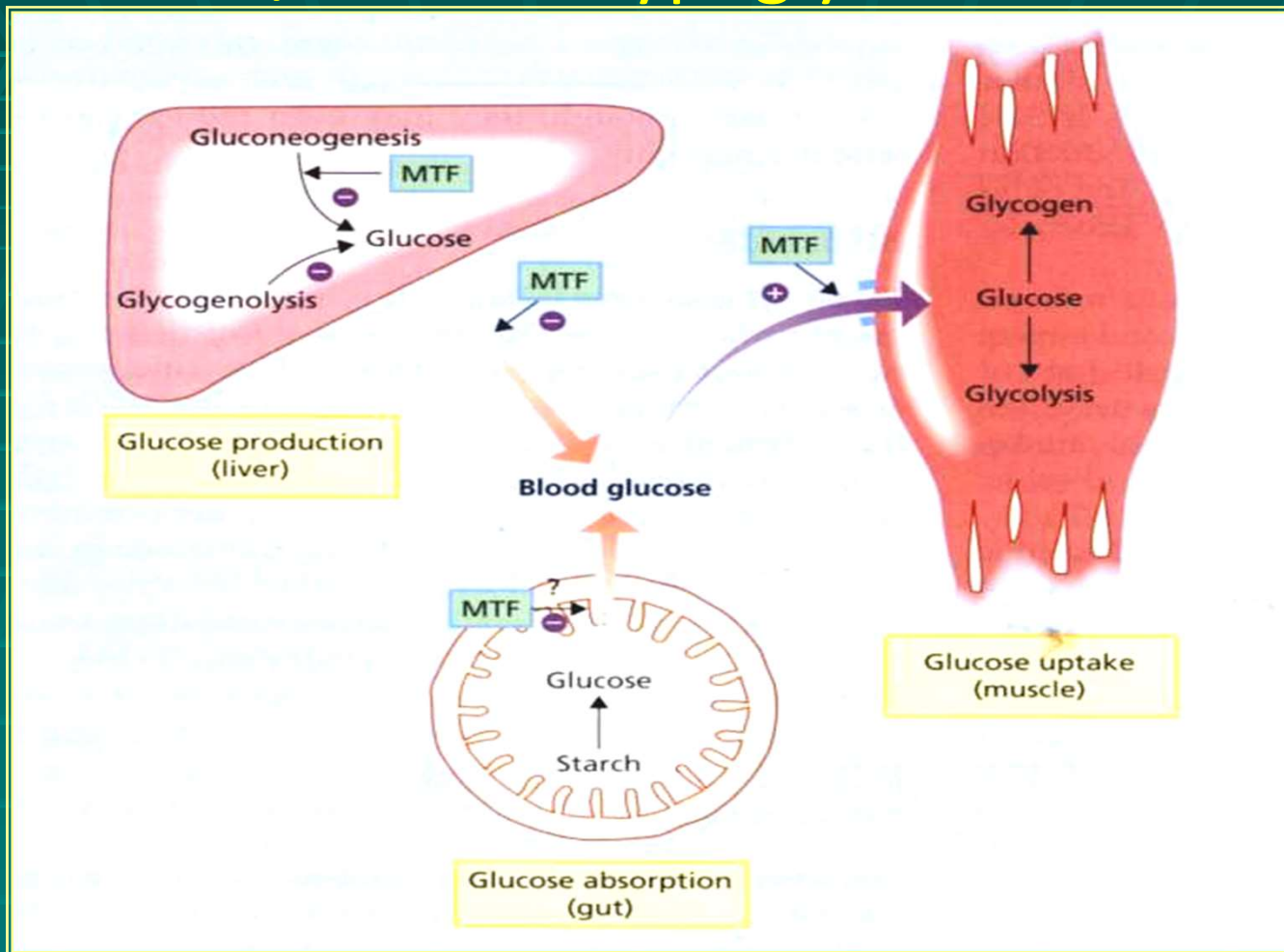
Metformin (glucophage)

– 1st line Tx for DM II

- *Metformin* is a biguanide substance with antihyperglycemic properties that is used for treating non – insulin – dependent diabetes mellitus. This drug can improve glucose levels in blood by decreasing the production of glucose in liver, decreasing intestinal absorption of glucose and increasing insulin-mediated glucose uptake. Induces weight loss.

3 main beneficial actions of metformin w/o risk of hypoglycemia

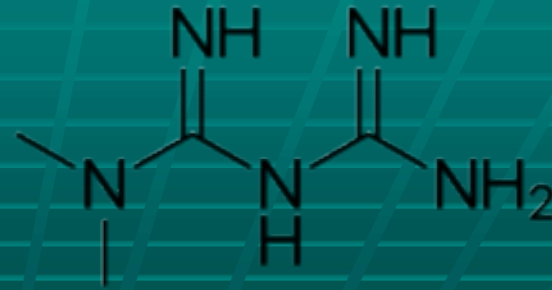
Decrease
by 24-36%





*Galega
officinalis*

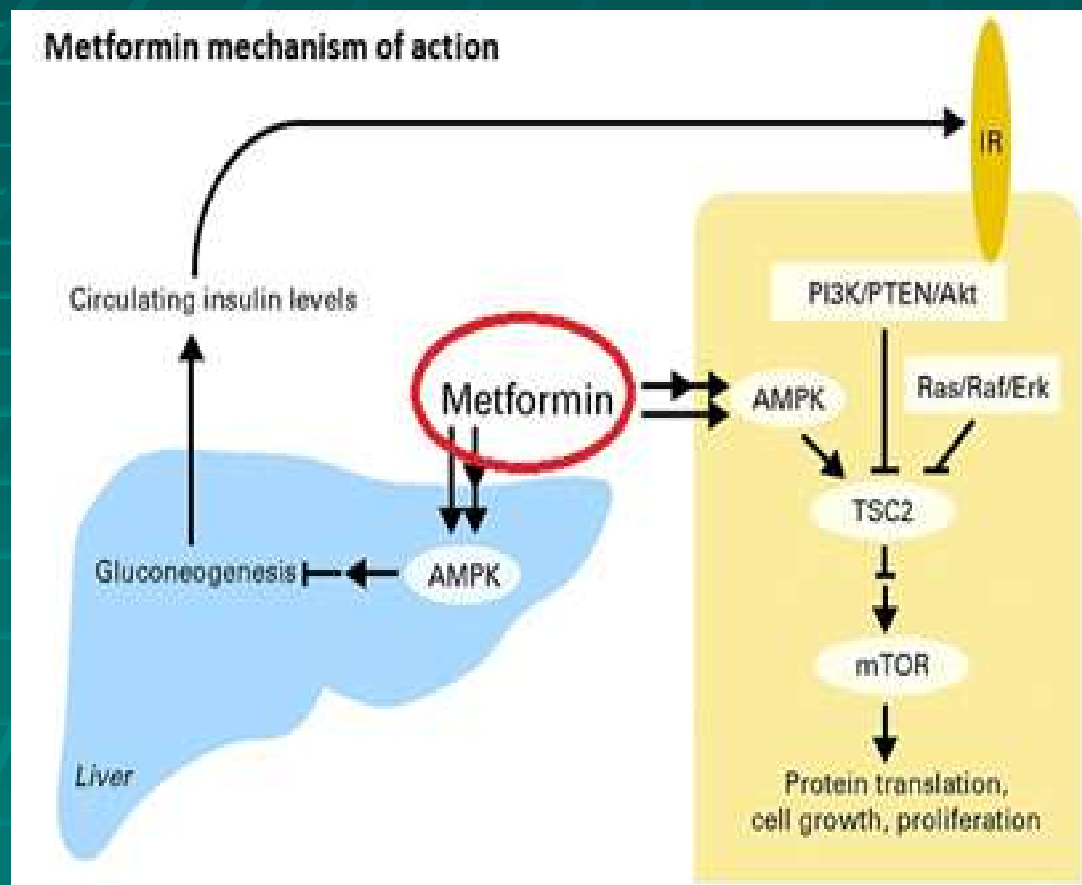
History



1. Biguanides- used in **early medieval times**-
leguminosa Galega officinalis (goat's rue or
French lilac) in Europe
2. 1928-guanidine discovered as active glucose-
lowering compound
3. 3 biguanides available for medical use
between 1957 & 1960- phenformin,
metformin, buformin
4. 1970s- phenformin and buformin withdrawn
because of lactic acidosis

Metformin activates an enzyme called AMPK

AMP-activated protein kinase



Important role in

1. Insulin signaling
2. Systemic energy balance
3. Metabolism of glucose and fats.

May explain why diabetics prescribed metformin have sharply lower cancer rates. risk of **pancreatic cancer** was **62% lower** in diabetics who had taken metformin compared to those who had never taken it. (MD Anderson)

Metformin

Slashes the risk of cancer

- Romero IL, McCormick A, McEwen KA, et al. Relationship of type II diabetes and metformin use to ovarian cancer progression, survival, and chemosensitivity. *Obstet Gynecol.* 2012 Jan;119(1):61-7.
- Li D, Yeung SC, Hassan MM, Konopleva M, Abbruzzese JL. Antidiabetic therapies affect risk of pancreatic cancer. *Gastroenterology.* 2009 Aug;137(2):482-8.

Lowers markers of vascular disease.

Brame L, Verma S, Anderson T, Lteif A, Mather K. Insulin resistance as a therapeutic target for improved endothelial function: metformin. *Curr Drug Targets Cardiovasc Haematol Disord.* 2004 Mar;4(1):53-63.

Reduces glucose production and the rate of **gluconeogenesis** by **24%** to **36%**
lowers A1C

Lowers the amount of insulin that is chronically secreted by pancreas

500 mg three times a day of metformin reduces insulin levels by **25%**.

Enhances insulin sensitivity

Reduces **triglycerides**,

Metformin – Efficacy for microvascular complications

1. 1704 obese type 2 diabetics with FPG > 6 mmol/lit after dietary trial
 2. Randomised to metformin to maintain FPG <6 vs “conventional” Rx with diet
 3. 10 year follow-up
-
1. 32% reduction in diabetes related endpoint
 2. 42% reduction in diabetes related death
 3. 36% reduction in all cause mortality

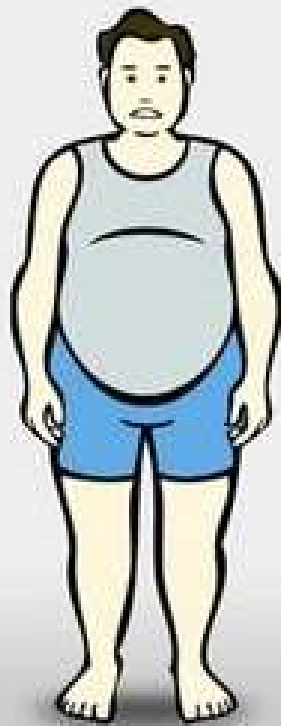
Metformin, causes favorable changes in the gut microbiota in patients with type 2 diabetes.

- Metformin boosts the capability of the bacteria to produce certain types of short-chain fatty acids, such as butyric acid and propionic acid.
 - These fatty acids can reduce blood glucose levels
 - Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. *Nature*, 2015; DOI: [10.1038/nature15766](https://doi.org/10.1038/nature15766)



**WHY IS TYPE DIABETES II
SKYROCKETING OUT OF CONTROL
AND AMERICANS IN SUCH POOR
HEALTH ?**

Why this matters – Same Dz, Different Specialists & Pharmaceuticals



THE METABOLIC SYNDROME



HEART DISEASE



LIPID PROBLEMS



HYPERTENSION



TYPE 2 DIABETES



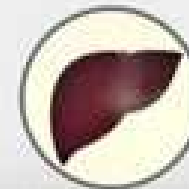
DEMENTIA



CANCER



POLYCYSTIC
OVARIAN
SYNDROME

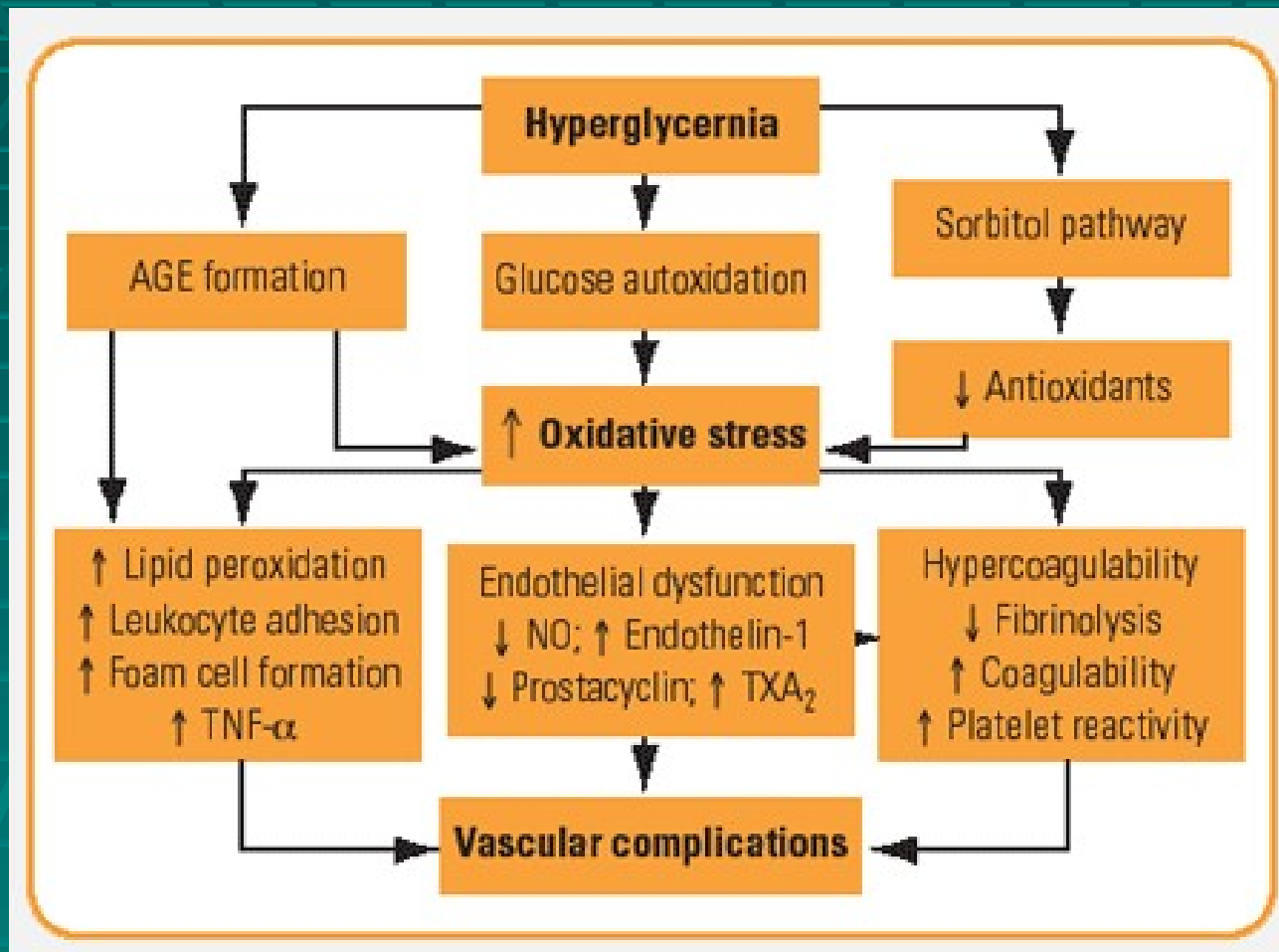


NON-ALCOHOLIC
FATTY LIVER
DISEASE

FBS guidelines too high ?

- Small elevations in glucose levels
 - **Increase cardiovascular mortality, strokes, kidney disease and retinopathy**, even if the glucose levels are not considered to be in the diabetic range (Whitehall Study UK, 1978)
- FBS > 85mg/dL equals
 - **40% increased risk of death from myocardial infarction (MI)** (Diabetes Care, 1999)
- Women w/FBS > 84mg/dl
 - > 2x the risk of **breast cancer** Vs < 84 mg/dl (Cancer Epi Bio Prev)

Hyperglycemia & Vascular Complications from ↑ blood sugar



Professor Thomas C Washer, Karl-Franzens University of Graz, Austria,
Understanding Diabetes, Oxidative Stress and Vascular Complications in type 2 diabetes

Increase Health Risk in People with “Normal FB Glucose”

Developing type 2 DM risk	100-104	Up to 283%
Stomach Cancer risk	95-105	up to 130%
First Time MI	Above 88	242% risk
Need for coronary bypass or stent	Above 95	73% risk

Elevated BS occurs late in a continuum of disease

- Patient w/ BS 105, FBI 35, 2hr Insulin 64 ?
- Could have elevated Insulin levels for 20-30 years but not be classified as having diabetes



Type 2 diabetes is caused by fat accumulating in the pancreas -- and that losing less than one gram of that fat through weight loss reverses the diabetes.

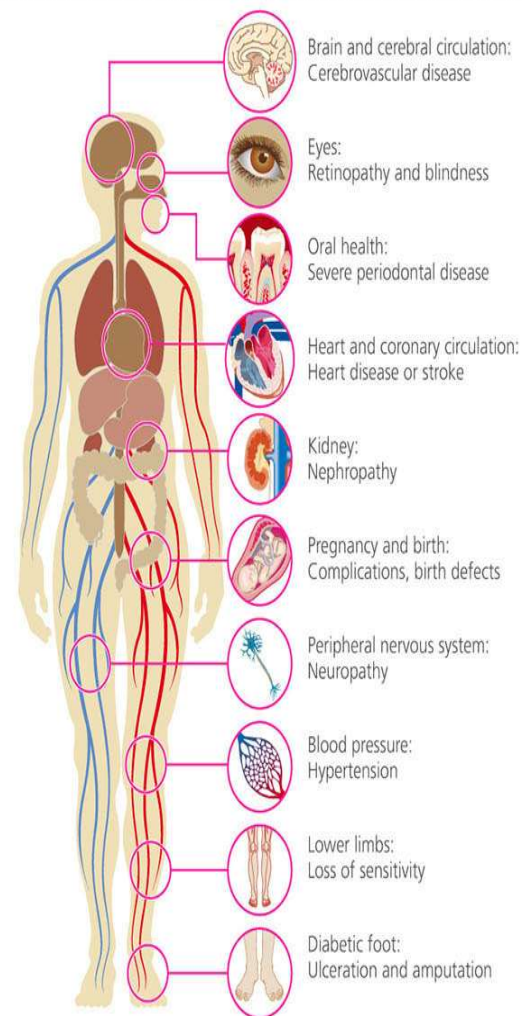
- Diet could remove fat clogging up the pancreas allowing normal insulin secretion to be restored. (Taylor 2011)
- level of fat in the pancreas is related to the presence of Type 2 diabetes
- increase in fat in the pancreas is specific to people who develop Type 2 diabetes.
 - Importantly, individuals vary in how much fat they can tolerate in the pancreas before Type 2 diabetes occurs.
- Patients who had never had diabetes saw no change in the level of fat in their pancreas demonstrating that the increase in fat in the pancreas is specific to people who develop Type 2 diabetes
- Decrease in pancreas fat is specific to Type 2 diabetes
- Regardless of your present body weight and how you lose weight, the critical factor in **reversing your Type 2 diabetes is losing that 1 gram of fat from the pancreas.**
- Type 2 diabetes is caused by fat accumulating in the pancreas -- and that losing less than one gram of that fat through weight loss reverses the diabetes.
- Weight Loss Decreases Excess Pancreatic Triacylglycerol Specifically in Type 2 Diabetes. Diabetes Care, December 2015 DOI: 10.2337/dc15-0750

Diabetes Associations

- Cancer
 - 20-30% increase risk of cancer
- Weight gain
- Thrombosis
 - MI and Stroke
 - Calcified arteries
 - Elevated blood platelet adhesiveness
- Retinopathy
- Kidney damage
- Increase estrogen in men &
- increase T in women
- Neuropathy
- Hypothyroid
- Abnormal lipids
- **Alzheimer's**

Complications & Effects of Diabetes

Diabetes is the leading cause of kidney failure, blindness, and non-traumatic amputation in adults.



Diagnosed diabetes cases cost the US
\$174 BILLION
in 2007

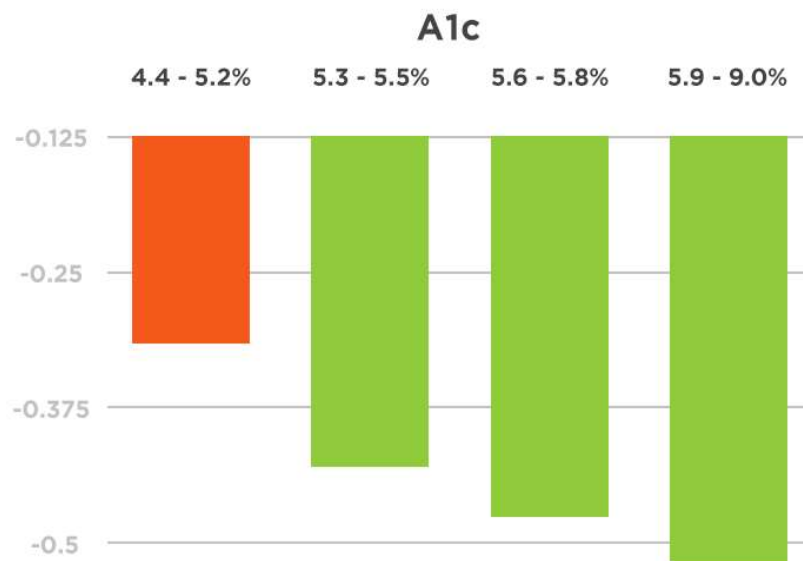
Implications of Pre-Diabetes/IR/PPG

High postprandial glucose (PPG)

- High postprandial glucose (PPG) of **157 to 189**
 - **Doubles** the risk of **congestive heart disease** as compared to PPG of **<144** (Diabetes, 1987)
- The risk of **MI** increases by **58% for** every **21** mg/dL increase in PPG (Circulation, 1995)
- **CVA inc 13% for each 18mg/dl** elevation in PPG
 - (Stroke 1995)
- Patients w/ “normal glucose levels” whose
 - **PPG >194mg/dl**
 - **3x** more likely to have **DR** (So Med Jr 2001)
- **Sudden death doubled** w/ PPG **>225mg/dl** (Circulation 1995)

HbA1c vs. Brain Shrinkage a continuum

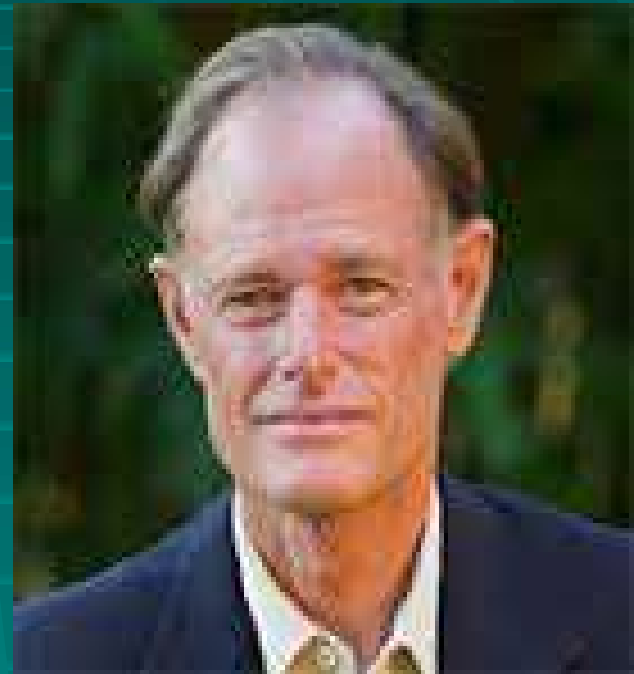
ANNUAL BRAIN SHRINKAGE



NEUROLOGY 64: 1704-11; MAY 24, 2005

 davidperlmutter MD

#GRAINBRAIN



Cause of Type 2 DM

Too much Insulin causing IR

- Mostly from empty calories
- Quickly absorbed sugars that spike Insulin
 - Bread, Potatoes, Pasta
- S/E
 - ↑ appetite, sugar cravings, belly fat, inflammation, inc BP, lipids, **blood thickening**

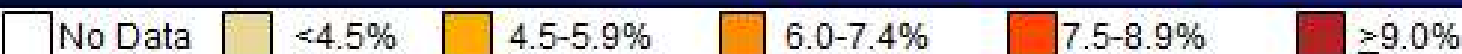


Age-adjusted Percentage of U.S. Adults Who Were Obese or Who Had Diagnosed Diabetes

Obesity (BMI ≥ 30 kg/m²)



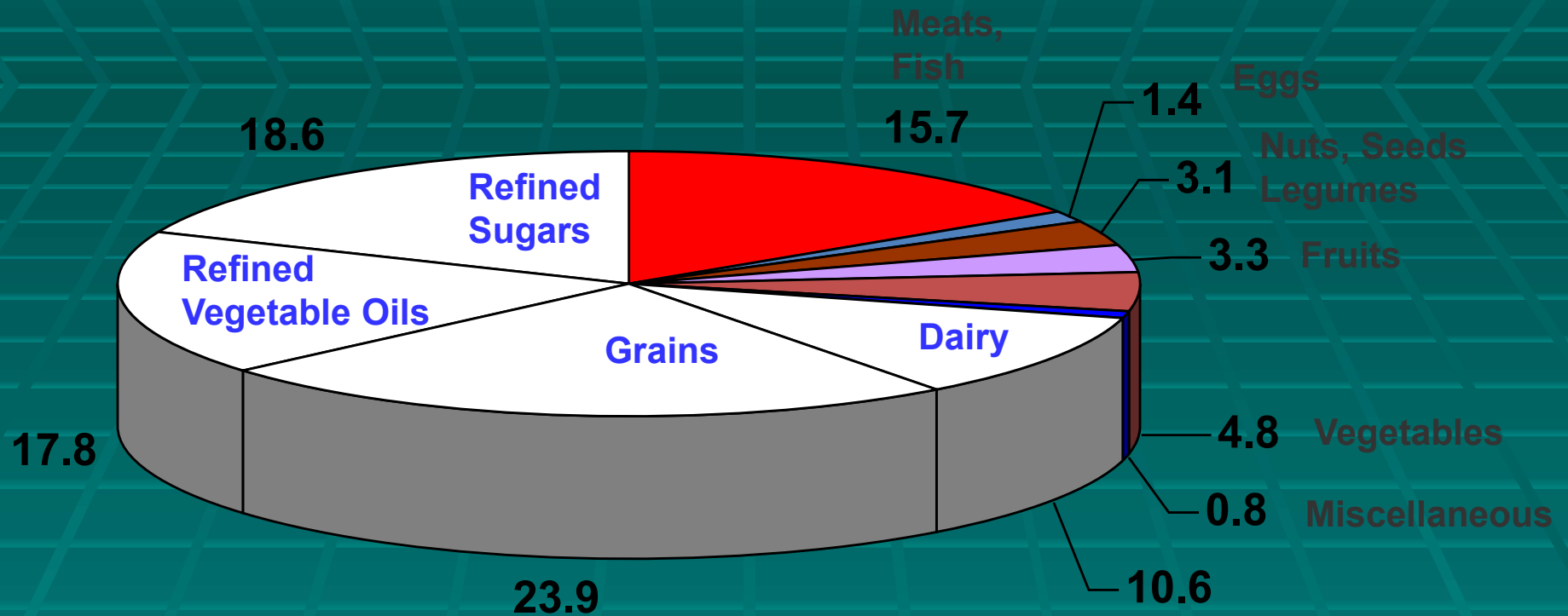
Diabetes



CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at <http://www.cdc.gov/diabetes/statistics>



Refined sugars, grains, vegetable oils and dairy = 70.9% of energy in the U.S. food supply



- Refined sugars, grains, vegetable oils and dairy represent Neolithic & Industrial era foods that were not present in traditional ancestral human diets
- By default, their inclusion displaces minimally processed, wild plant and animal foods.

Diabetes Mellitus

- Type I
 - 8-10% of all cases of Diabetes
 - Autoimmune condition
 - Destruction of β -cells
 - Insulin production reduced
 - Toxicity from high glucose levels
 - Up to 8 decade of life
 - (LADA) Latent autoimmune DM in adults
- Type II
 - 90% of all cases of diabetes
 - Toxicity from both high insulin and high blood sugars
 - Development of insulin resistance
 - Decrease in insulin receptors
 - Metabolic defect of receptors
 - Decreased production by β -cells (“pancreas burns out”)

TV Ads For Children

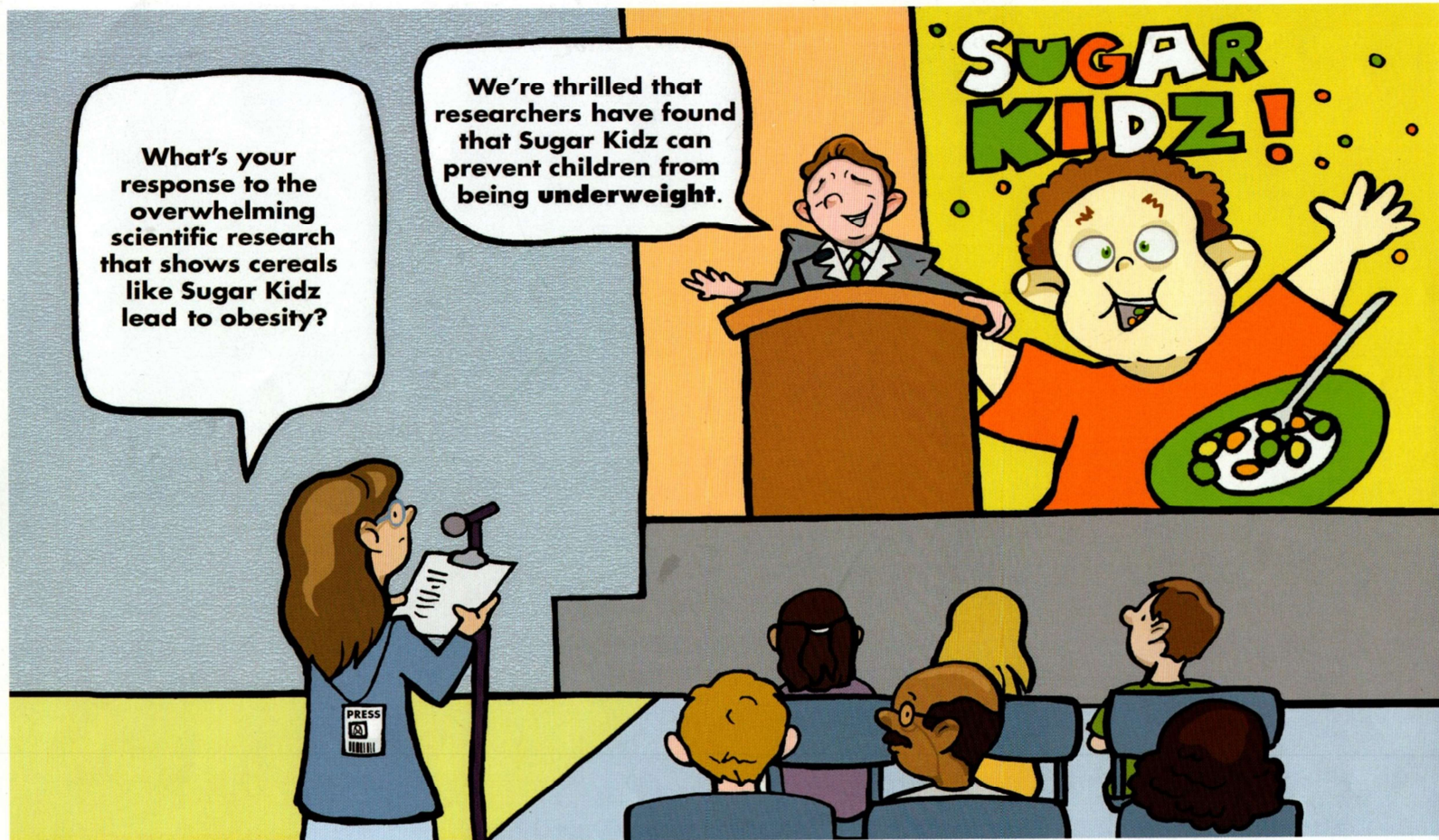


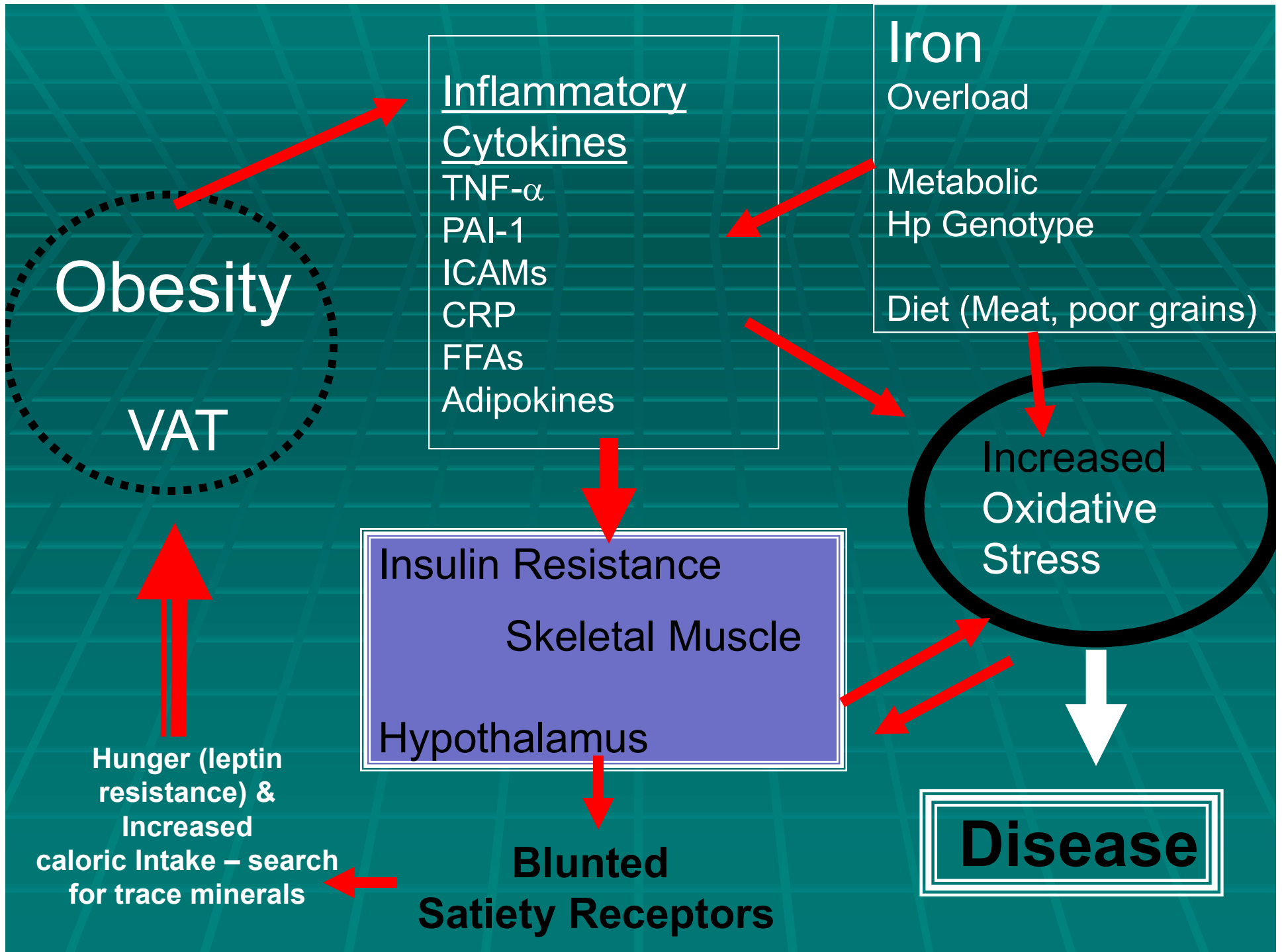
- 40 percent of the ads kids see on television are for sugary snacks
 - Research shows these early impressions can significantly shape their future food habits.



- Dr. Jennifer A. Emond Geisel School of Medicine at Dartmouth

Union of Concerned Scientists



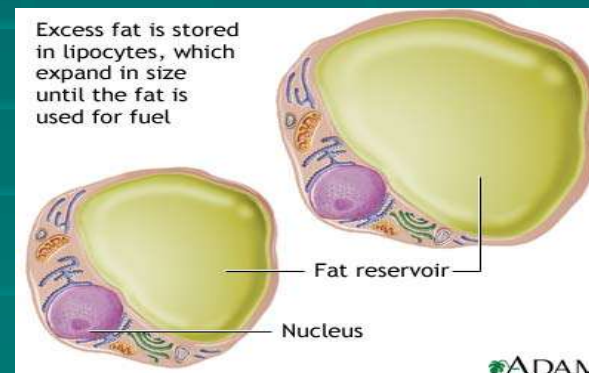
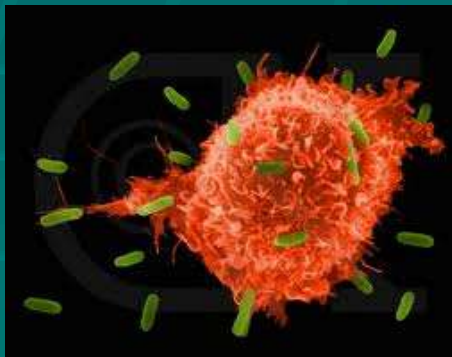


Chronic inflammation precedes Type 2 DM

VAT is an Endocrine Gland



- Belly fat releases adipokines (cytokines)
 - i.e. leptin - 1st discovered in 1994
 - TNF Alpha increases IR by desensitizing insulin receptors
 - Adipose tissue contains many macrophages



While it is true that....

Obesity linearly increases Risk Type 2 DM

- Upper range of the normal distribution of weight 3-5x risk compared to people in low range
- **Seriously obese** 50-100x the risk
- Not all obese individuals have high insulin or IR



We are measuring the wrong parameter

% Body Fat is superior to BMI



Body Mass Index (BMI)
Weight in Pounds (lbs) and Kilograms (kg)

	100 lbs 45 kg	110 lbs 50 kg	120 lbs 54 kg	130 lbs 59 kg	140 lbs 63 kg	150 lbs 68 kg	160 lbs 73 kg	170 lbs 77 kg	180 lbs 82 kg	190 lbs 86 kg	200 lbs 91 kg	210 lbs 95 kg	220 lbs 100 kg	230 lbs 104 kg	240 lbs 109 kg	250 lbs 113 kg
4'0"	22	25	26	29	31	34	36	38	40	43	45	47	49	52	54	56
4'1"	22	24	26	28	30	33	35	37	39	41	43	45	48	50	52	54
4'2"	21	23	25	27	29	31	34	36	38	40	42	44	46	48	50	52
4'3"	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	51
4'4"	20	22	23	25	27	29	31	33	35	37	39	41	43	45	47	49
4'5"	19	21	23	25	26	28	30	32	34	36	38	40	42	44	45	47
4'6"	18	20	22	24	26	27	29	31	33	35	37	38	40	42	44	46
4'7"	18	20	21	23	25	27	28	30	32	34	35	37	39	41	43	44
4'8"	18	20	21	22	24	26	28	29	31	33	34	36	38	40	41	43
4'9"	18	20	21	22	23	25	27	28	30	32	33	35	37	38	40	42
4'10"	18	19	21	22	24	26	27	29	31	32	34	36	37	39	41	43
4'11"	18	19	20	21	23	24	26	27	29	30	32	34	35	37	39	40
5'0"	18	19	20	21	22	24	25	27	28	30	31	33	35	36	38	39
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5'10"	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33
5'11"	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33
6'0"	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33
6'1"	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33
6'2"	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33

Legend: ■ Healthy Weight ■ Overweight ■ Obese

Body fat percentage chart

Classification	Men Body Fat %	Women Body Fat %
Essential	2 – 4	10 – 12
Athletes	6 – 13	14 – 20
Fitness	14 – 17	21 – 24
Acceptable	18 – 25	25 – 31
Obese	> 25	> 31

<http://healthiack.com>

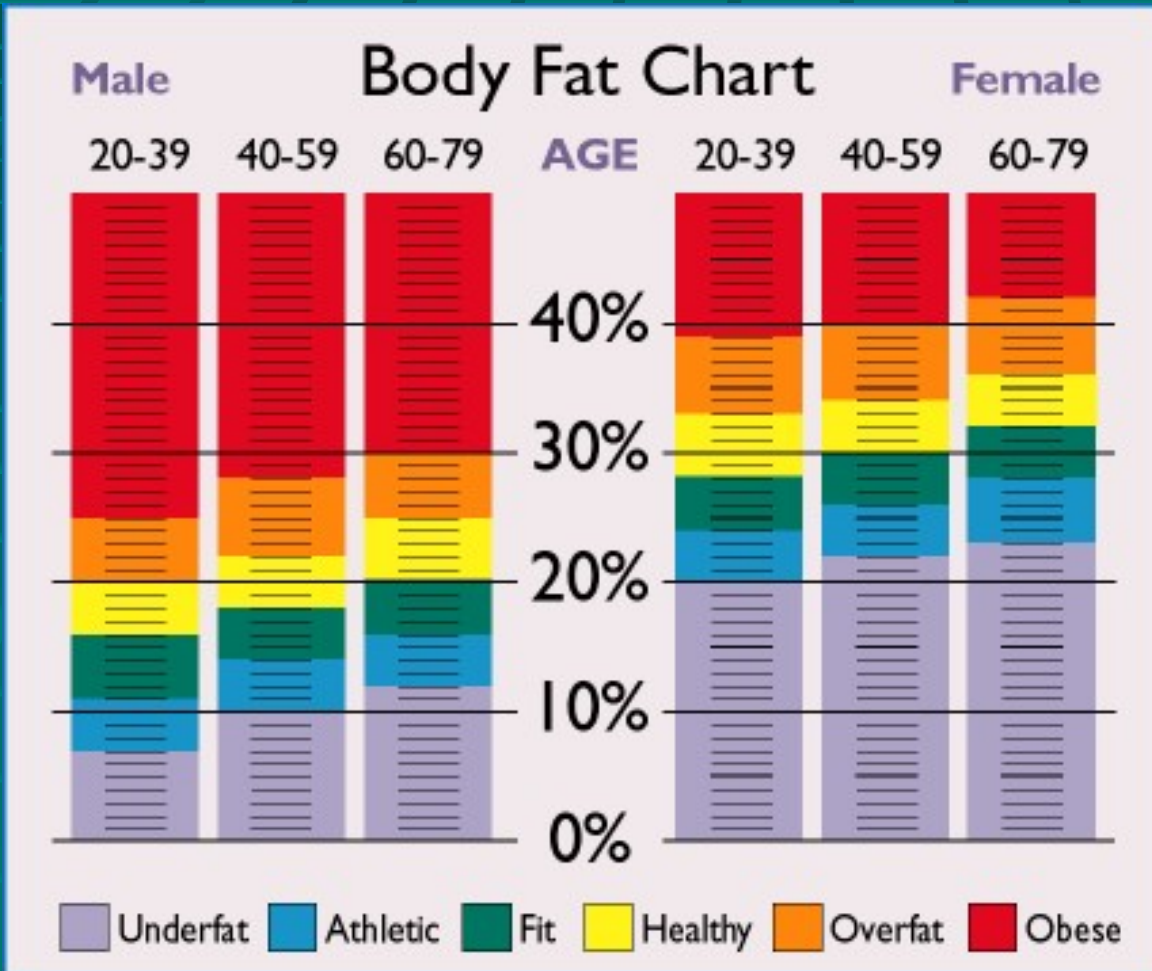
BODY MASS INDEX (BMI)

CLASSIFICATION	BMI SCORE (kg/m ²)
Underweight	< 18.5
Normal	18.5 - 24.9
Overweight	25.0 - 29.0
Obese	30.0 - 40.0
Extreme Obese	> 40.0

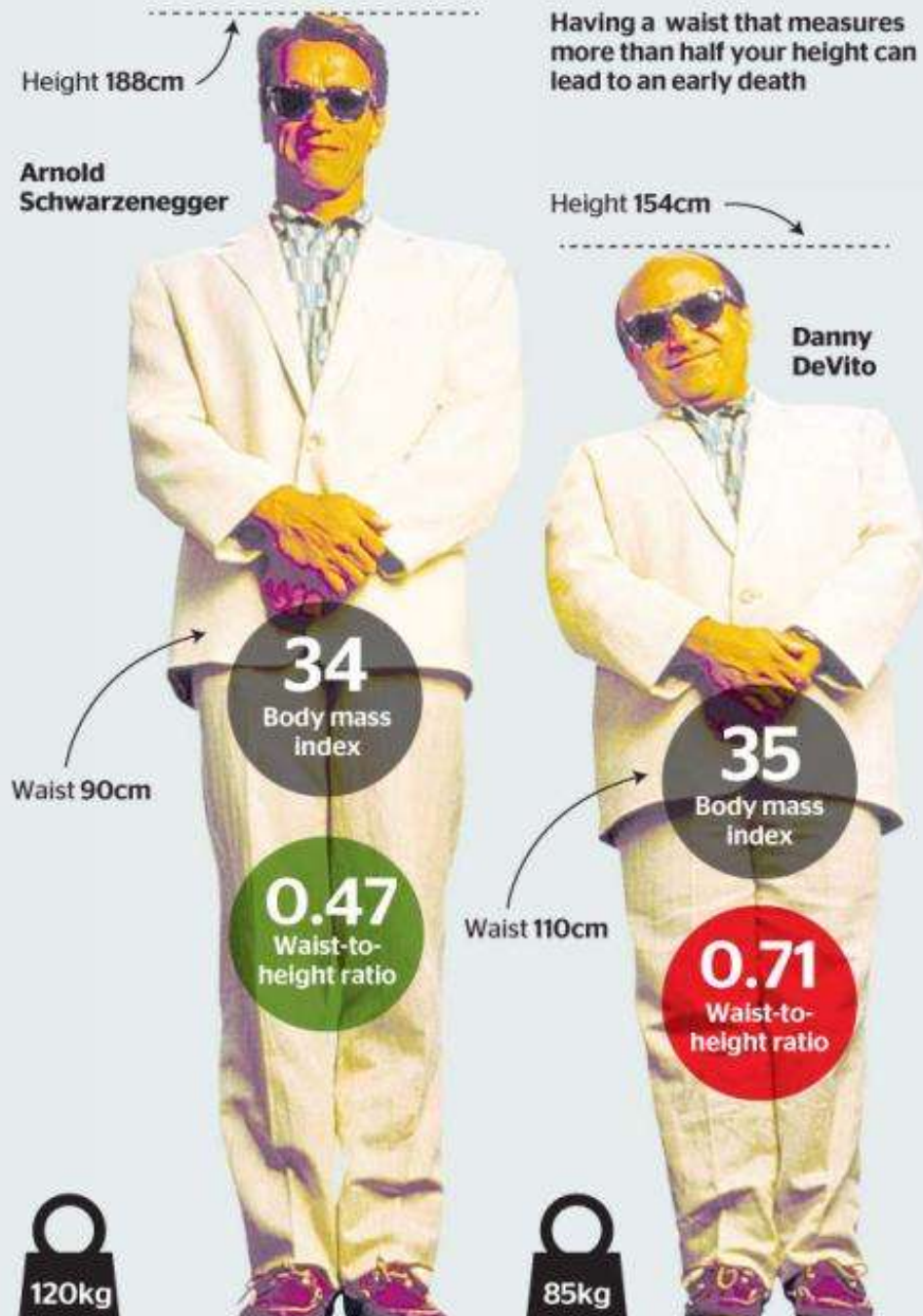
www.cdn.lifebuzz.com

% Body Fat superior to BMI

i.e. Non Alcoholic Fatty Liver Disease (NAFLD)

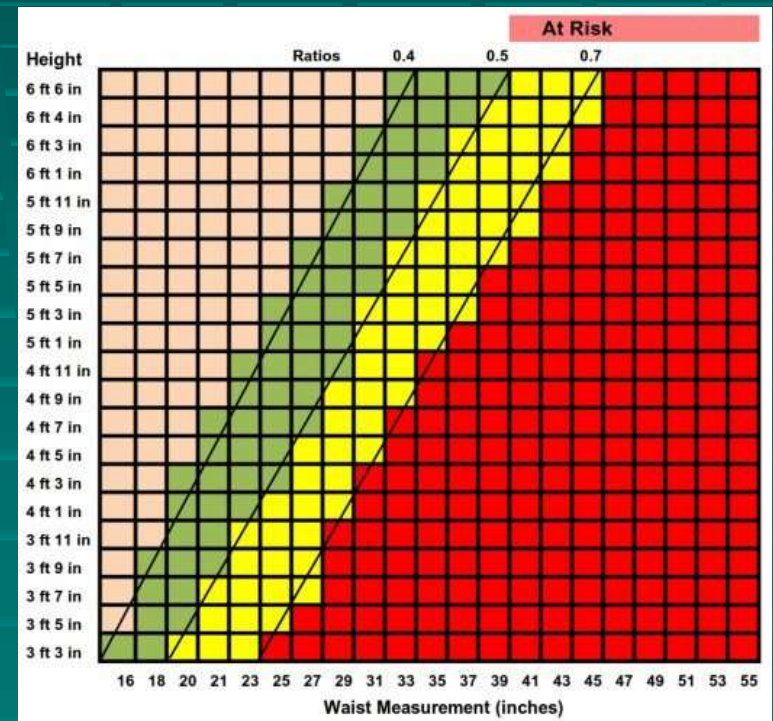


Measure for measure



WhtR

Waist /Height ratio Correlates with INSULIN SENSITIVITY



Source: Margaret Ashwell

<https://usercontent2.hubstatic.com/8>

[001831_f520.jpg](https://usercontent2.hubstatic.com/8001831_f520.jpg)

www.thetimes.co.uk

- A 30-year-old obese man with a high **waist-to-height ratio** of about 0.8, has a predicted loss of 16.7 years or life expectancy
- A 30-year-old woman with a similarly high **waist-to-height ratio** of about 0.7 has a predicted loss of 9.5 years or life expectancy
- For obese men and women aged 50 years the average reduction in lifespan is about 10 and 5 years respectively.
- **People with the very high waist-to-height ratios of 0.8 (waist circumference was 80% of their height) were expected to have their lifespans reduced by an average of 17 years.**

Visceral Fatty Tissue

(think % body fat, not BMI)



1. insulin increases the synthesis of fatty acids from glucose.
2. insulin facilitates the entry of glucose into adipocytes
3. insulin inhibits breakdown of fat in adipocytes.

KEY ---adipose tissue is known to secrete various metabolites, hormones and cytokines that play a role in causing hyperinsulinemia

Visceral Fatty Tissue

+ Adiponectin Metabolic Effects

- **glucose flux**
 - decreased gluconeogenesis
 - increased glucose uptake
- **lipid catabolism**
 - β -oxidation
 - triglyceride clearance^l
- Protects from endothelial dysfunction (important facet of atherosclerotic formation)
- Promotes insulin sensitivity
 - weight loss
 - control of energy metabolism.
 - upregulation of uncoupling proteins
 - reduction of TNF-alpha
- **Regulation of adiponectin**
 - *****Obesity is associated with decreased adiponectin.**
 - The exact mechanism of regulation is unknown, but adiponectin could be regulated by post-translational mechanisms in cells.

A Stealth Disease processes

*No visible symptoms of
hyper-insulinemia
unless low blood sugar
is present and most do
not measure % body*

Hypoglycemia

- Temporary muscle weakness
- Brain fog
- Fatigue
- Temporary thought disorder, or inability to concentrate
- Visual problems such as blurred vision or double vision
- Headaches
- Shaking/Trembling
- Thirst

over- sweating

- Gluten intolerance
 - Wheat / rye / barley / oats
 - Loose 85 -95% of absorptive surface of small intestine
 - Cannot absorb n3 fats so high risk of thrombosis
 - Cannot absorb micronutrients ie. minerals well
 - Drop in blood sugar induces sweating

Hyperglycemia

Blood sugar rises above normal if

1. ↓ in insulin secretion (endogenous)
2. ↓ in insulin sensitivity (non-response)
3. ↑ increased hepatic production
4. ↓ decreased peripheral utilization
5. Excessive CHO consumption
6. A combination of any of the above

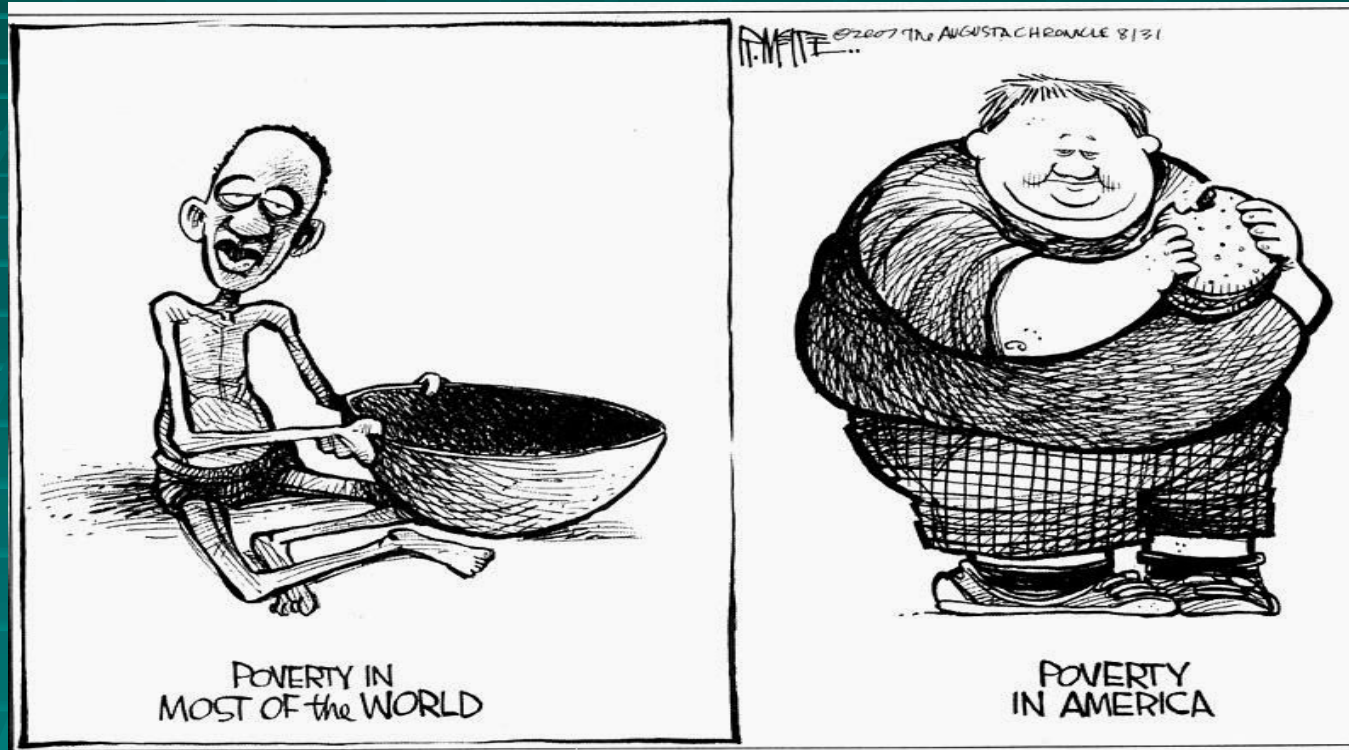


Robert Lustig MD



The dogmatic belief that "a calorie is a calorie" has significantly contributed to the ever-worsening health of the Western world. It's one of the first things dieticians learn in school, and it's completely false. In reality, the source of the calories makes all the difference in the world when it comes to health. (Mayo Clinic Proceedings 2015)

The poorest people in the US have the highest obesity rates.




It's also true that most Americans exercise too little, but it's important to realize that **you simply cannot exercise your way out of a poor and metabolically "toxic" diet.**

Soda is most popular SNAP expenditure item (48 million Americans)

- Nurses Health Study
- Women who drank **one soda** per day **nearly doubled** their risk of DM
- Average American drinks **52 gallons** per year



2nd most popular SNAP item (48 million Americans)



Calories from bread, refined sugars, and processed foods promote overeating, whereas calories from whole vegetables, protein, and fiber decrease hunger.

Standard American Diet (SAD)

- 92% deficient in 1 or more essential vitamins and minerals
- 70%-80% deficient in Vitamin D
- > 90% deficient in essential omega 3 fatty acids



Dr. Robert Lustig

*“.. Science should drive policy, but the politics gets in the way....and politics is based on money. **The food industry nets about \$450 billion per year, yet America wastes at least \$830 billion per year caring for diseases linked to metabolic syndrome... This is unsustainable, and a major reason why Medicare and Social Security will be broke by 2030. The USDA must do the right thing and curb Americans' consumption of added sugar, rather than kowtowing to the processed-food industry.**”*

Principal Drivers of Diabetes



- “We clearly showed that sugar is the principal driver of diabetes,” James J. DiNicolantonio, a cardiovascular research scientist at Saint Luke’s Mid America Heart Institute.
- “A sugar calorie is much more harmful.” *Mayo Clinic Proceedings 2015*
- Once you reach 18% of your daily calories from sugar there's a **two-fold increase in metabolic harm** that promote prediabetes and diabetes

**Americans consume anywhere
between 150 to 170 pounds of
refined sugars in one year**

**Average
American
consumes
32
(5 lb bags)
of sugar /
year**



Replacing Refined Sugars and Processed Fructose

By replacing refined sugars and processed fructose with starches, obese children (aged 8-18) saw significant improvements in biomarkers associated with health in just 10 days,

- Even though their overall calorie intake and the overall % of carbohydrates remained the same.
- Reducing the amount of added sugars from an average of 27 % of daily calories down to about 10 %
Isocaloric fructose restriction and metabolic improvement in children with obesity and metabolic syndrome Robert H. Lustig

Replacing Refined Sugars and Processed Fructose with Starch

- On average, children (aged 8 to 18) saw improvements in their lab work and disease markers after this short intervention:
 - LDL cholesterol fell by 10 points
 - Diastolic blood pressure fell 5 points
 - Triglycerides were reduced by 33 points
 - Fasting blood sugar dropped by 53 %
 - Insulin levels also significantly improved

Isocaloric fructose restriction and metabolic improvement in children with obesity and metabolic syndrome Robert H. Lustig

Dr. Robert Lustig

*"Every aspect of their metabolic health got better, with no change in calories (or exercise). **This study definitively shows that sugar is metabolically harmful** not because of its calories or its effects on weight. Rather, sugar is metabolically harmful because it's **sugar.**"*

1st menstruation occurred earlier among girls with the highest consumption of drinks sweetened with added sugar.

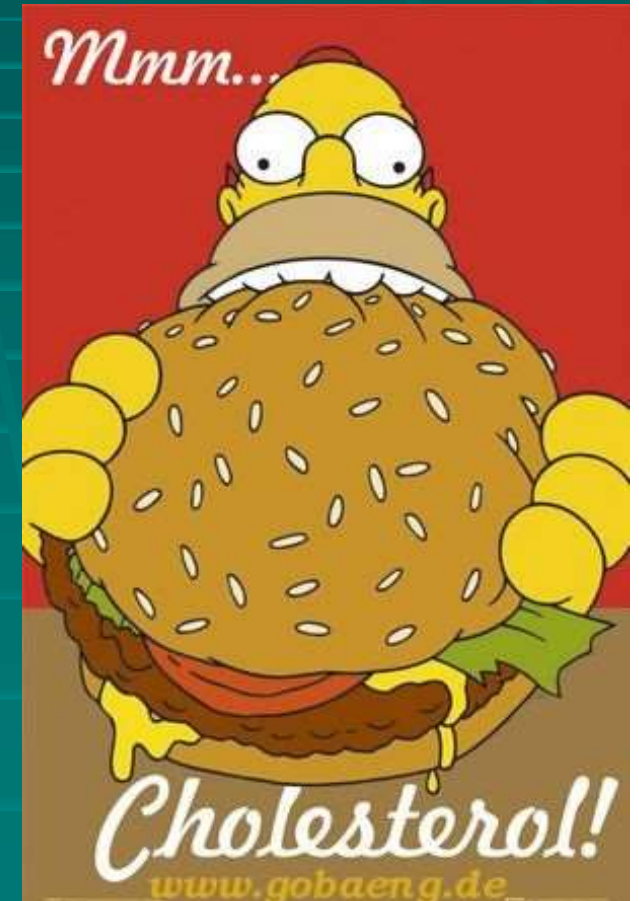
- Independent of body mass

"Our study adds to increasing concern about the widespread consumption of sugar-sweetened drinks among children and adolescents", Karin Michels who ,studies links between environmental exposures, genetics and disease.

Nurses Health Study

90,000 nurses 16 years

- 91% of type 2 DM caused by
 - Unhealthy diet
 - Lack of exercise



The increase in diabetes in last 10 years is not just lack of exercise and poor diet

1. Genetic predisposition – minimal factor.

It is becoming increasingly clear that up to 90% of our disease risk stems from our environment, not genes. (Lichtenstein NEJM, 2000)

2. Sedentary lifestyle

Sitting for more than eight hours a day raises your risk for type 2 diabetes by 90% (tAnn Intern Med. 2015;162(2):123-132)

3. Caloric excess

4. Sarcopenia (lack of muscle mass so one can't process glucose properly)

5. Micronutrient deficiencies (Mg, B6, Vit D, Chromium, carnitine) can impair fat loss

The odds are 80% of being over weight if micronutrient deficient (econ hum bio 2007) Nutrient deficiencies cause cravings and weight gain

6. Junk food

- (Fructose is correlated with metabolic syndrome and type 2 diabetes). Study from 2009 within 2 weeks supplementing pts with large doses of fructose and they developed diabetes.
- Average American consumed about 35.7 pounds of high-fructose corn syrup Illinois Farm Bureau,
- Trans fats

Causes of Type 2 DM/MS

Increase in diabetes in last 10 years not just lack of exercise and poor diet

- 7. Xenobiotic exposure = pollutants such as dioxins and polychlorinated biphenyls and their effect on the micro biota
 - Accumulation affects **aryl hydrocarbon receptor** which **down regulates the expression of peripheral glut-4 glucose insulin receptors thus leading to peripheral insulin resistance**. This points to the importance of detoxification as a role in treatment and as a prevention in lifestyle.
 - Avoid exposure
 - Detox
 - Promote plant based diet making urine alkaline ,,,,like when hospital gives IV sodium bicarbonate for toxin overdose like aspirin
 - Probiotics ,B6, MG, NAC, chlorella (after meals)
 - IR saunas
- 8. Systemic inflammation contributes directly to IR
 - Lipoic acid, improves gut dysbiosis, wt loss and abdominal obesity,
- 9. Gut dysbiosis – antibiotics, gluten, GMO

Diet Beverages with Artificial Sweeteners no better

- **Adults with diabetes**
 - **Who drank 1 or more drinks of diet soda per day**
 - **A1C levels were 0.7 % higher than those who drank none..**
- Promotes insulin resistance and is also pro-inflammatory.
- **Doubles the risk of Metaboic syndrome**
- **Wt gain**



Diet of Beverages with Artificial Sweeteners

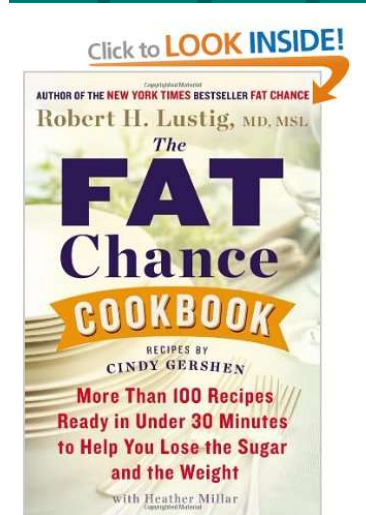
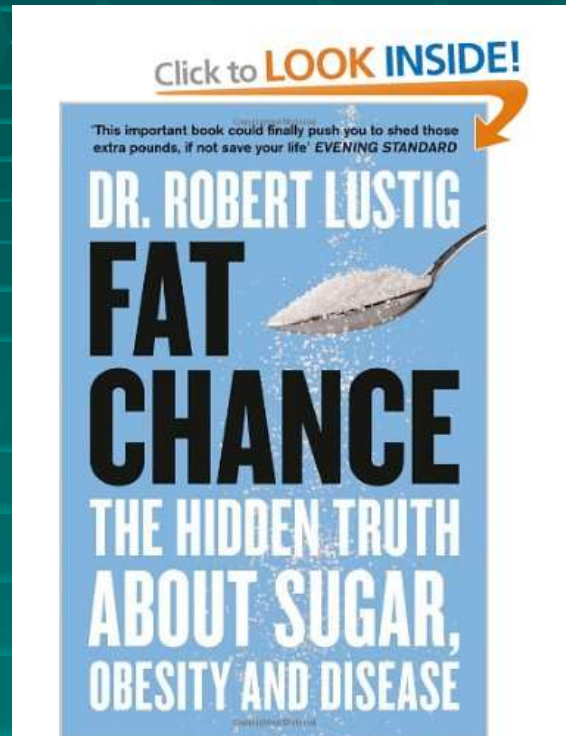
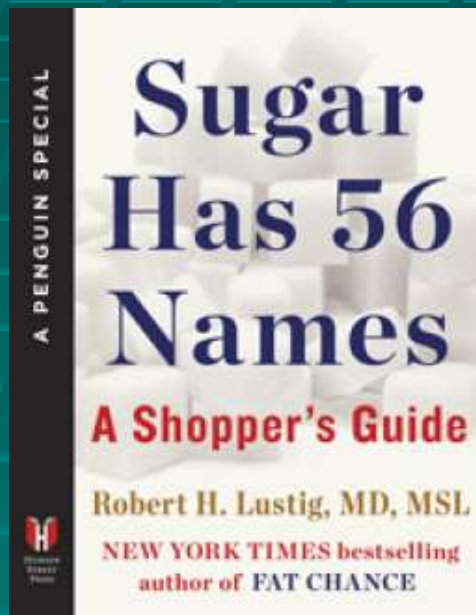
- Since advent of **artificial sweeteners**, rates of obesity and diabetes have continued to climb. Research over the past 30 years has repeatedly **shown they have very similar effects as regular sugar**, promoting both obesity and diabetes. Yale Journal of Biology and Medicine June 8 2010: v83(2)
- Some studies have even demonstrated that **artificial sweeteners worsen diabetes and obesity** to a greater degree than regular sugar and HFCS. UT Health Center San Antonio Press Release June 14, 2005
- For example, one 2012 study found that **saccharin and aspartame** both **cause greater weight gain than sugar**, even when the total caloric intake remains similar. Appetite January 1, 2012, Volume 60, Pages 203-207

Hyperinsulinemia / IR

- After smoking, **Hyperinsulinemia / IR** is most important measure of future health



A CALORIE IS NOT A CALORIE) Sugar (hfcs): The Bitter Truth



Robert H. Lustig, M.D., M.S.L.
Division of Endocrinology,
Department of Pediatrics
Institute for Health Policy
Studies
University of California, San
Francisco
Adjunct Faculty
UC Hastings College of the Law

It's about hepatic fat (NAFLD -fatty liver disease)
125 million Americans & metabolic dysfunction

“Our Food supply is contaminated”

Robert Lustig MD



- **Addition of Fructose**
 - Number one source of calories in US
- Approximately 77% of food items in US grocery stores contain added sugar.
- We have removed fiber
- We have substituted
Trans-fats



HFCS introduced in mid 1970's

- Cheaper sweetener than sucrose
- Fructose is 100% metabolized in liver to
 - Uric acid that blocks NO (nitric oxide)
 - HTN
 - 30% fructose / 0% of glucose becomes fat
 - Free radicals
- 7x more likely to glycate
- Doesn't suppress ghrelin
- Doesn't stimulate leptin

**JUST SAY NO
TO
HIGH
FRUCTOSE CORN
SYRUP**

Trans-fats

– finding a replacement ?

- In June of 2015, the US Food and Drug Administration (FDA) announced
 - Partially hydrogenated oils (a primary source of trans fat) will no longer be allowed in food
 - unless authorized by the agency due to their health risks.
- According to the FDA
 - Will prevent around 20,000 heart attacks and 7,000 heart disease deaths each year
 - The new regulation will take effect in 2018.
- Food industry **reverted back to using regular vegetable oils**, and this is far from an ideal replacement.
 - Especially when heated, vegetable oils
 - **Peanut, corn, and soy oil** degrade into highly toxic oxidation products that appear to be even worse than trans fats!
 - Ex. aldehydes **oxidize LDL cholesterol** and cause high levels of inflammation, which is associated with heart disease.

“Food” supply



- GMO

- Use of glyphosate, the active ingredient in Roundup, has significantly risen, with about one billion pounds being sprayed on crops each year. GE crops are far more contaminated with glyphosate than conventional crops
- Glyphosate was recently classified as a Class 2A “probable human carcinogen” by the World Health Organization’s (WHO) research arm on cancer, and the US Department of Agriculture (USDA) admits foods are not tested for glyphosate residues due to the high expense of doing so.

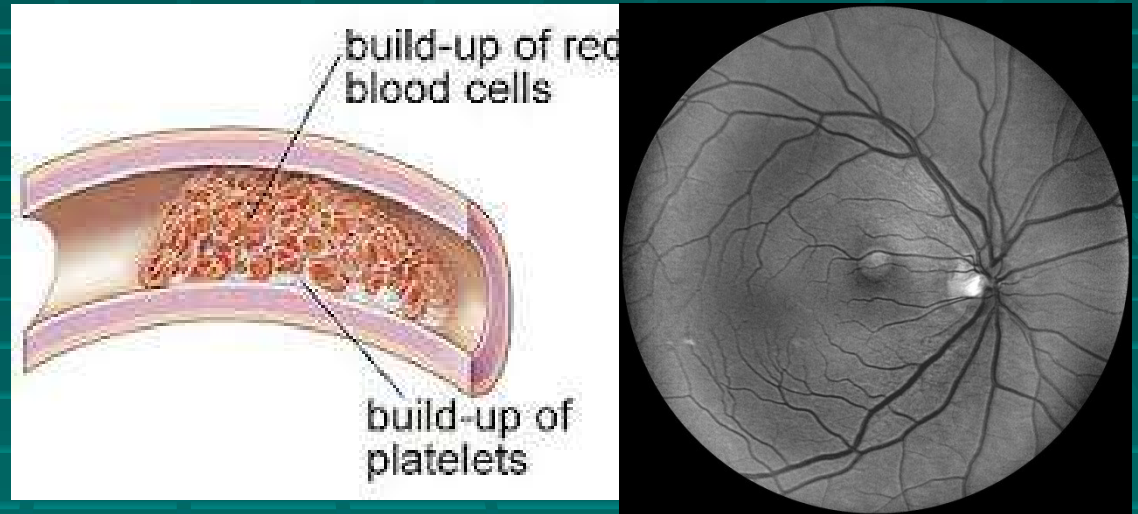
- Grown in nutrient - depleted soil
- Fertilized w petro chemicals
- Stored for months
- Shipped in boxes across 1000’s miles
- Filled with antibiotics
- Hormones pumped into livestock, fish
- Grained fed farmed fish CAFOs (Concentrated Animal Feeding Operations), where the beef, chicken or pigs are fed genetically modified corn and soybeans and excessive grains in general (which are not the natural diet of these animals).



EARLY CONCEPTS
“METABOLIC SYNDROME”
GERALD REAVEN, MD 1987
(STANFORD ENDOCRINOLOGIST)

Metabolic syndrome:

- * Central obesity
- Hyperglycemia
- HTN
- Dyslipidemia
- Systemic inflammation
- Hypercoagulability
- Hormone imbalances
 - men produce more estrogen
 - women produce more testosterone
- “Metabolic syndrome is more serious than diabetes or HTN alone b/c the constellation of problems accelerates the development of CVD and cancer (men-prostate; women-breast)”



Metabolic Syndrome

Table 1 Common definitions for metabolic syndrome

Criterion	NCEP ATP III ^a (3 or more criteria)	IDF ⁴⁰ (abdominal obesity plus 2 or more other criteria)
Abdominal obesity		
Men	> 40 inches	≥ 37 inches
Women	> 35 inches	≥ 31.5 inches
Hypertriglyceridemia	≥ 150 mg/dL	≥ 150 mg/dL
Low HDL		
Men	< 40 mg/dL	< 40 mg/dL
Women	< 50 mg/dL	< 50 mg/dL
Hypertension	≥ 130/85 mm Hg or on antihypertensive medication	≥ 130/85 mm Hg
Impaired fasting glucose or diabetes	≥ 110 mg/dL* or taking insulin or hypoglycemic medication	≥ 100 mg/dL

NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; IDF, International Diabetes Federation;
HDL, high-density lipoprotein.
*Recently lowered to 100 mg/dL.¹³

Jr Am Cardiology Metabolic syndrome
(MS) 2x risk of CVA, CVD, MI,
MS 2x risk of death all cause



Metabolic Syndrome

- NECP ATP III criteria – 3 or more below
 1. Abdominal obesity – W.C (cm) > 88 ♀, 102 ♂
 2. ↑ in Triglycerides > 150 mg%
 3. ↓ in HDL < 50 mg% for ♀, < 40 mg% for ♂
 4. Blood pressure > 130 / 85 mm Hg
 5. IFG = FPG > 110 or IGT = PPBG > 140 mg%
- WHO criteria (in addition to above)
 1. ACR (albumin / creatinine ratio) > 30 mg/g
 2. Micro-Albuminuria > 20 µgs / min

Metabolic Syndrome is associated with

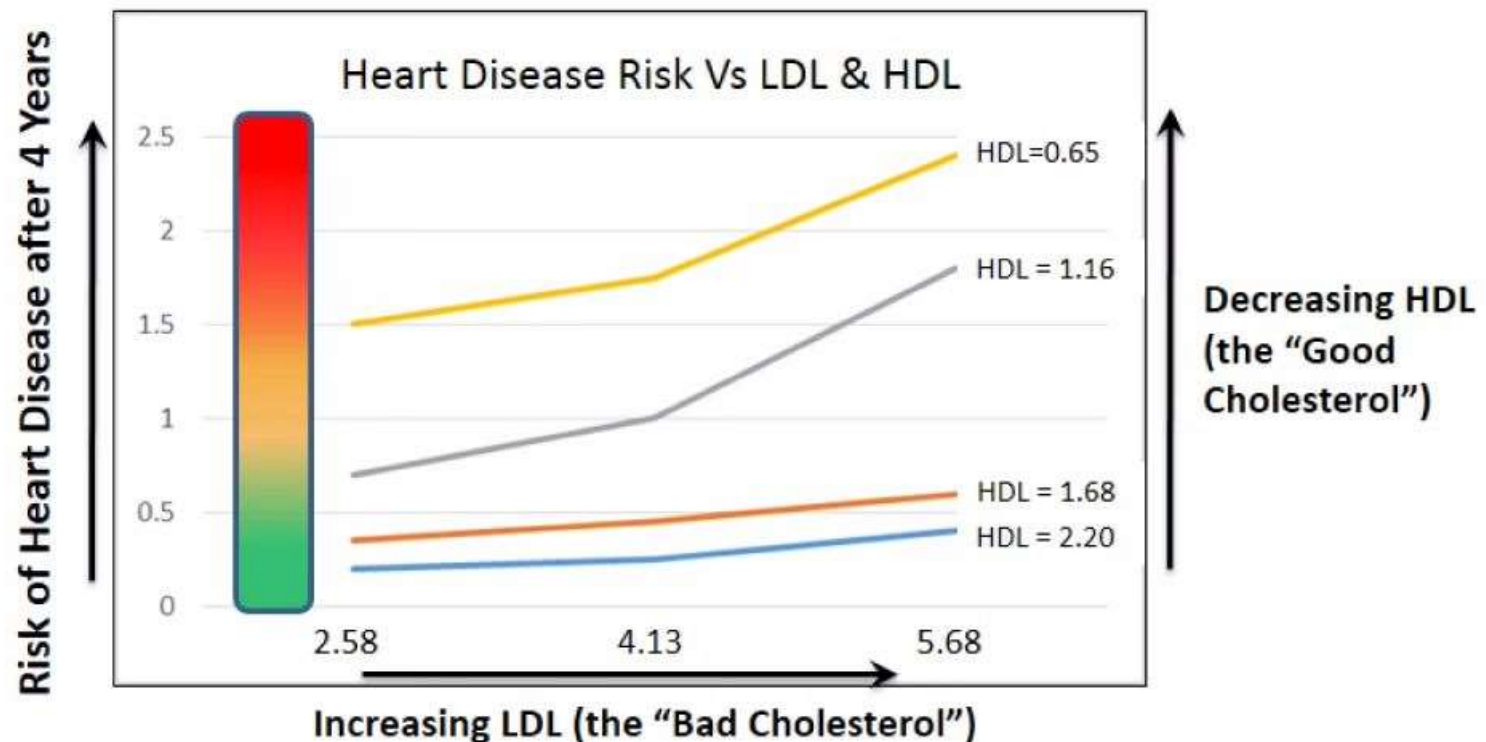
- NAFLD (non-alcoholic fatty liver disease)
- sdLDL (small dense LDL cholesterol)
- Oxidative stress
- Polycystic ovary syndrome
- GERD (gastroesophageal reflux disease)
- Sleep apnea
- Asthma
- Depression
- Osteoporosis
- Alzheimer's
- Cancers



Abdominal obesity causes

- Inflammation (CRP)
 - Greater waist > hsCRP
- Angiotensin
(vasoconstriction) BP increase
- Insulin resistance

LDL & HDL as predictive factors?

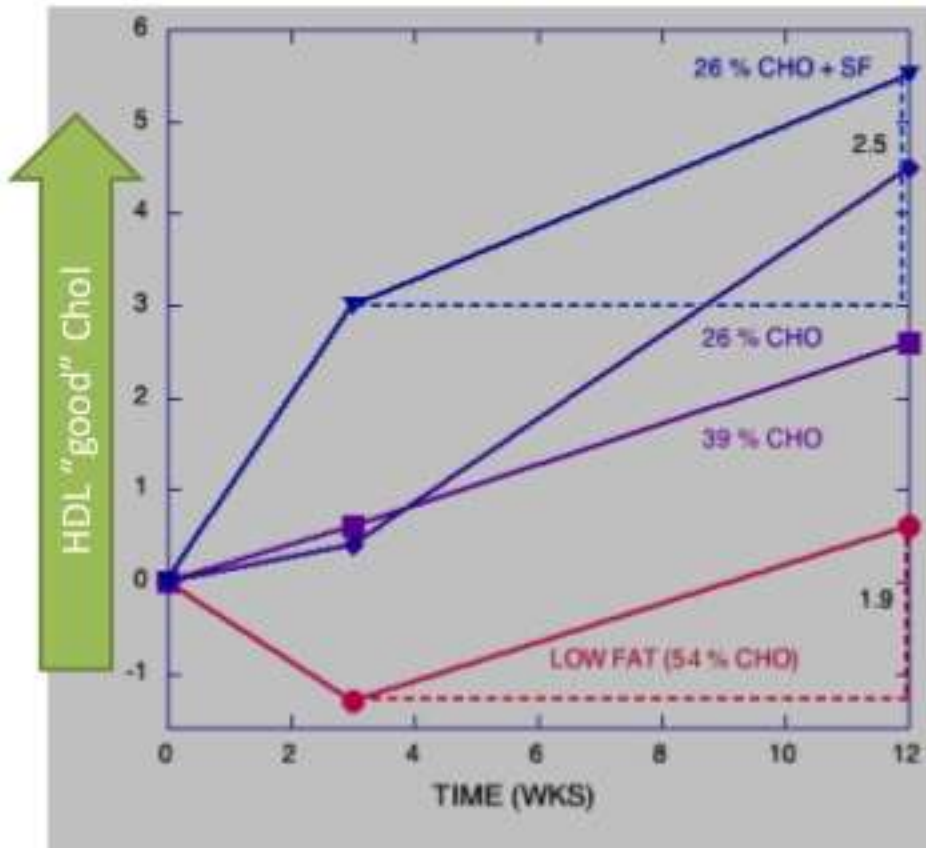


Data from the Framingham Heart Study showing incidence of CAD over 4 years in men 50-70 years old

Diagram adapted from article in Journal of Cardiovascular Medicine 2011, Vol 00, No 00

- ❖ HDL being adequate/higher is VERY important
- ❖ The benefit of LDL being low.....totally depends on the HDL status
- ❖ Risk is determined primarily by the **RATIO** of these parameters
- ❖ Diagnosing via LDL is minimally useful in the face of the current science

Improving HDL Levels



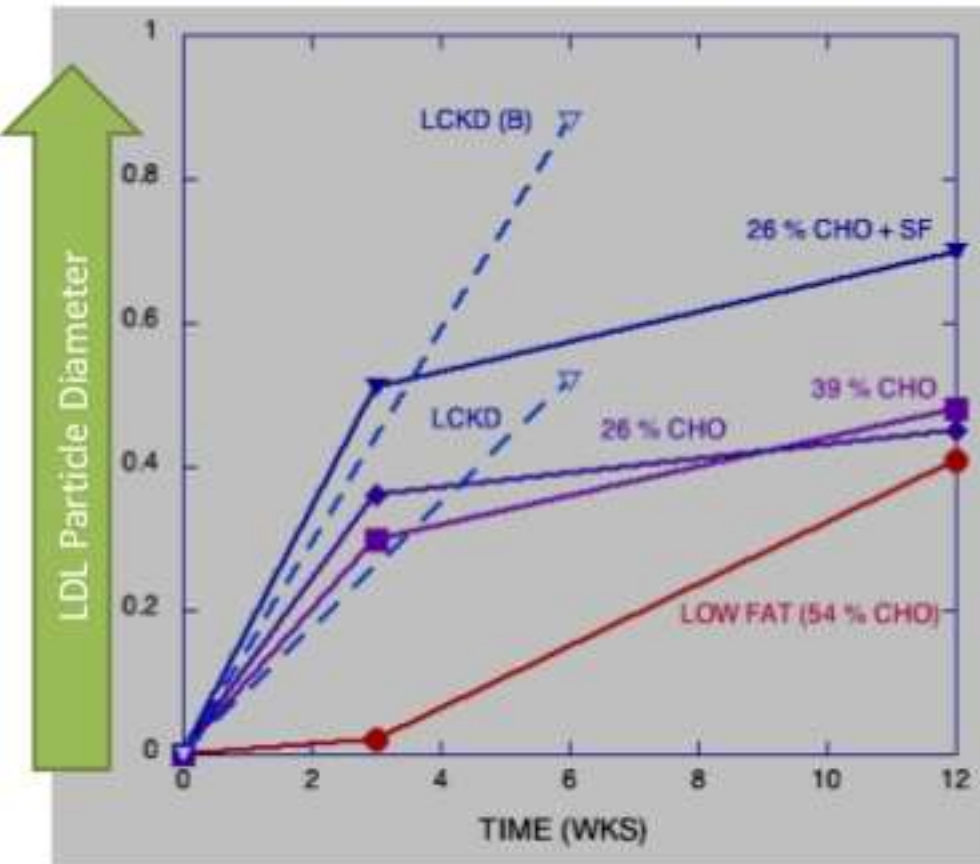
- ❖ HDL – the higher the better
- ❖ Increasingly Lower Carb delivers dose-response increased improvement
- ❖ Even during the starvation period, Low Fat regime fails
- ❖ Low Carb far exceeds benefits of low fat regime, again even with no dieting

Data adapted from from Jeff Volek Summary of:

Separate effects of reduced carbohydrate intake and weight loss on atherogenic dyslipidemia¹⁻³

Ronald M Krauss, Patricia J Blanche, Robin S Rawlings, Harriett S Femstrom, and Paul T Williams

Improving LDL Particle Diameter



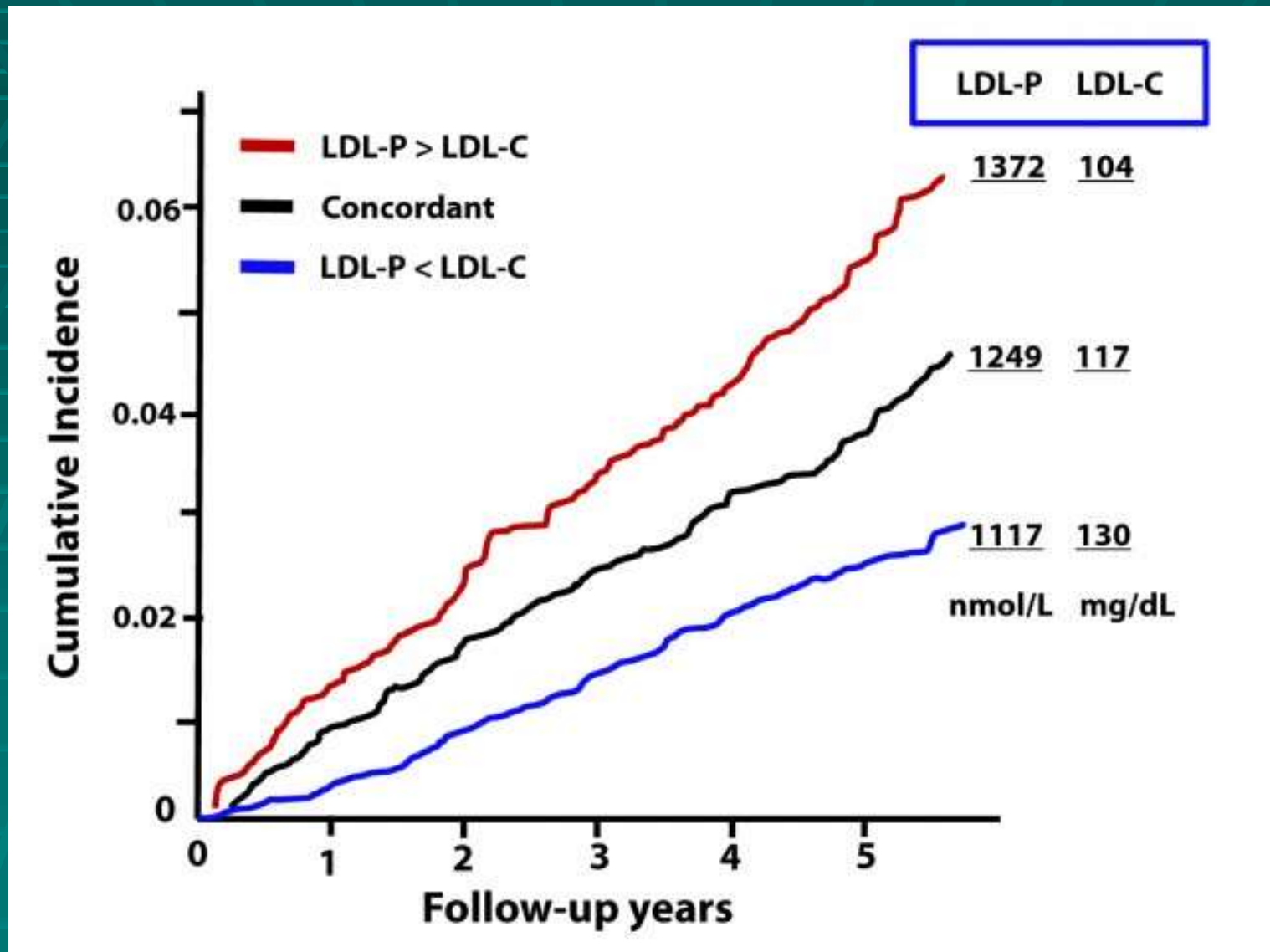
- ❖ LDL Particle Diameter is a serious metric
- ❖ Increasingly Lower Carb delivers dose-response increased improvement
- ❖ Even during the starvation period, Low Fat regime struggles
- ❖ Low Carb far exceeds benefits of low fat regime, especially if you don't diet

Data adapted from from Jeff Volek Summary of:

Separate effects of reduced carbohydrate intake and weight loss on atherogenic dyslipidemia¹⁻³

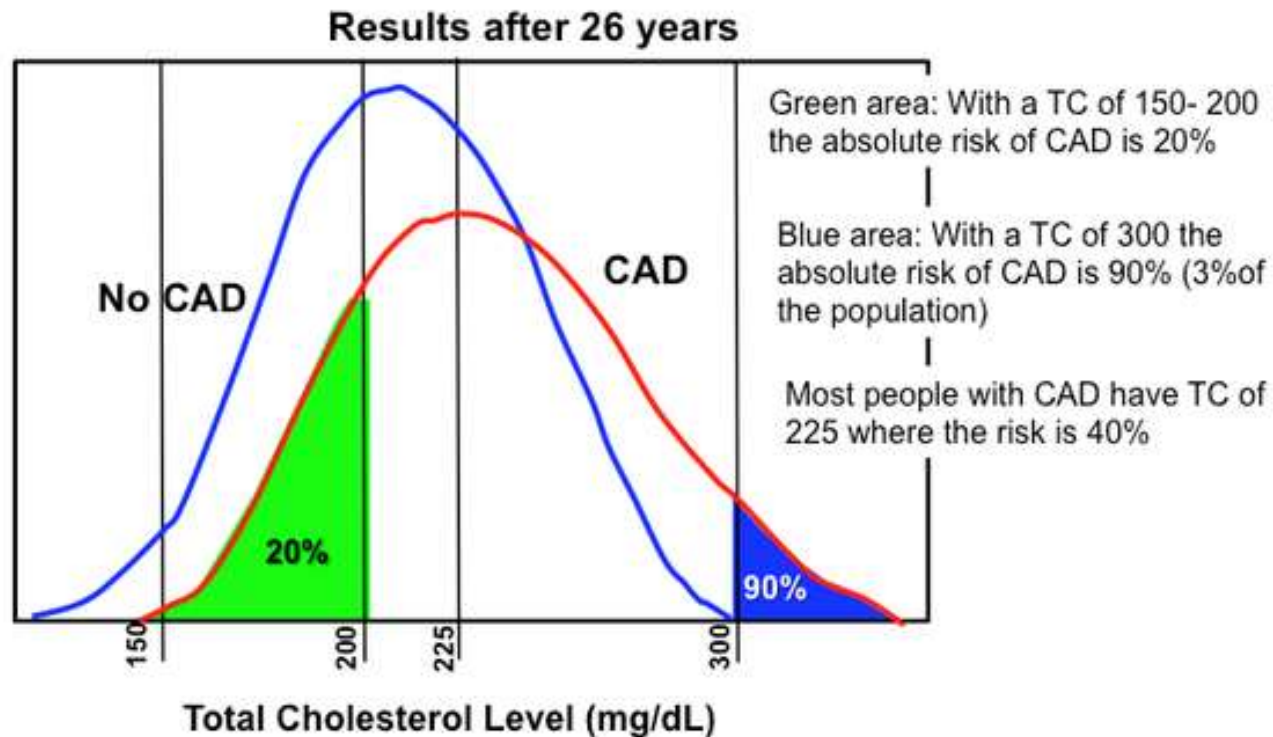
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Small dense LDL (sdLDL)



Triglycerides

Framingham Heart Study



Castelli, William. The American Journal Of Cardiology, 1998; 82: 60T-65T

Everything In Moderation ?

FASEB July 21, 2015 [Epub ahead of print]

- Eating just **one junk food treat per day for one month** is enough to trigger **metabolic syndrome in healthy people**.
- The treats, which provided an additional 1,300 calories per day, included an assortment of candy bars and pasties

