# Blood Sugar and Insulin Stabilization

**Dr. Joseph Pizzorno, ND**

**President Emeritus, Bastyr University**

**Editor, *Integrative Medicine: A Clinician's Journal***

**Chair, Science Board, Bioclinic Naturals**

**President, SaluGenecists, Inc.**

# Dr. Joseph E. Pizzorno, N.D.

- **Academic**
  - **Founding president (1978) of Bastyr University, first accredited, natural medicine university**
  - **Editor-in-Chief: *Integrative Medicine: A Clinician's Journal***
  - ***Textbook of Natural Medicine*, 3nd ed. 2004; 4th edition now in process**
- **Policy**
  - **Member Medicare Coverage Advisory Committee, 2003-2005**
  - **Member White House Commission on CAM Policy, 2000-2002**
- **Public**
  - ***Encyclopedia of Natural Medicine*, 1998 (1,000,000 copies in six languages)**
  - ***Encyclopedia of Healing Foods*, 2005**
- **Example Awards and Recognitions**
  - **Juror for Roger's Prize – 2009, 2011**
  - **Institute for Functional Medicine – Linus Pauling Award, 2004**
  - **American Holistic Medical Association: *Pioneer in Holistic Medicine*, 2003**
  - ***Natural Health Magazine*: *Leading health educator in the past 30 years*. 2001**
  - **Alternative Healthcare Management: *1 of the 4 most influential CAM leaders*, 2000**
  - ***Seattle Magazine*: *1 of the top 20 national intellectual leaders from Seattle*, 1996**

# Outline

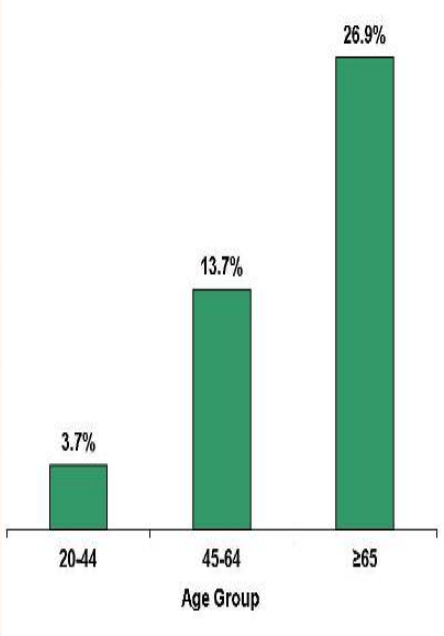
- Epidemiology
- Spectrum of insulin resistance/beta cell failure
- Pathophysiology/Contributing factors
- Clinical Implications
- Assessment
- Treatment

# Related Diseases

- Metabolic Syndrome
- Obesity
- Pre-diabetes
- Type I diabetes
- Type II diabetes
- PCOS (polycystic ovarian syndrome)
- Alzheimer’s disease
- Cardiovascular disease

# Epidemiology

- For 2010, the CDC reported that approximately 25.8 million people, or 8.3% of the U.S. population, have diabetes, with about 1/4 unaware of it; that number is expected to double by 2050
- NHANES 2005-2006: among non-diabetic adults, 34.6% had pre-diabetes
  - 19.4% had impaired fasting glucose only
  - 5.4% had impaired glucose tolerance only
  - 9.8% had both IFG and IGT
- Thus, over 40% of individuals have diabetes or pre-diabetes
- NHANES 1999-2002, prevalence of Metabolic syndrome (MetS) in the United States is 39% among men & women ≥ 20




CDC 05-08

http://www.cdc.gov/diabetes/pubs/estimates11.htm#1
Karve A, Prevalence, diagnosis, and treatment of impaired fasting glucose and impaired glucose tolerance in nondiabetic U.S. adults. Diabetes Care. 2010 Nov;33(11):2355-9.
Ford ES. Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. Diabetes Care. 2005 Nov;28(11):2745-9.

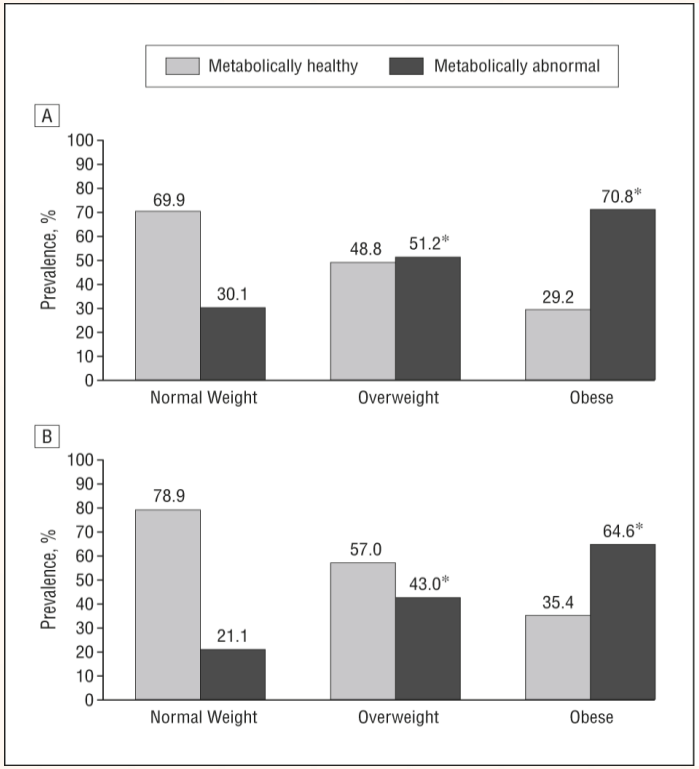
# Metabolic Syndrome

- **A 9-fold increase for T2D with 3 components present, up to an astounding 33.67-fold increase with all present**
  - **Hyperglycemia**
  - **Hypertension**
  - **Elevated BMI**
  - **Abnormal total or HDL cholesterol**
  - **Proteinuria**
  - **Hyperuricemia**
- **Children with Met-S have 15-fold risk for cardiovascular disease as adults**
- **Study of 1,200 Finnish men found a 2.9-4.2–times risk of dying of coronary heart disease, after adjusting for conventional risks**

Klein BE, et al. Components of the metabolic syndrome and risk of cardiovascular disease and diabetes in Beaver Dam. Diabetes Care. 2002 Oct;25(10):1790-4.
Morrison JA, et al. Metabolic syndrome in childhood predicts adult cardiovascular disease 25 years later: the Princeton Lipid Research Clinics Follow-up Study. Pediatrics. 2007 Aug;120(2):340-5
Lakka HM, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA. 2002 Dec 4;288(21):2709-16.

# Obesity is a Driver for Metabolic Dysfunction

- NHANES 2009/10:
  - The age-adjusted prevalence of obesity was 35.5% among adult men and 35.8% among adult women (adults over 20)
  - 73.9% of men were either overweight or obese, as were 63.7% of women
  - Almost 17% of children and adolescents were obese
- Obesity independent risk factor metabolic dysfunction




Wildman 2008

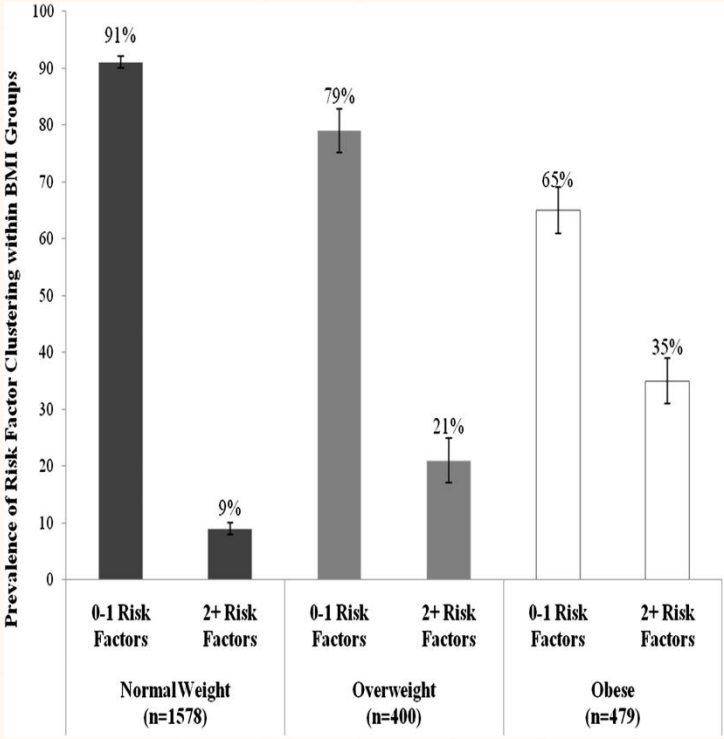

Flegal KM, et al. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. JAMA. 2012 Feb 1;307(5):491-7.

Ogden CL, et al. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. JAMA. 2012 Feb 1;307(5):483-90.

Wildman RP, et al. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004). Arch Intern Med. 2008 Aug 11;168(15):1617-24.

# Obesity & Risk Factor Clustering in Children

- NHANES data (2001-2002, 2003-2004, 2005-2006, and 2007-2008)
- Total weighted prevalence for risk factor clustering was 15.8% (i.e. ≥2 risk factors: triglycerides; HDL; BP; fasting glucose
- Obese adolescents had the greatest prevalence (35%)
- For each unit of BMI z-score, 2x the odds for risk factor clustering

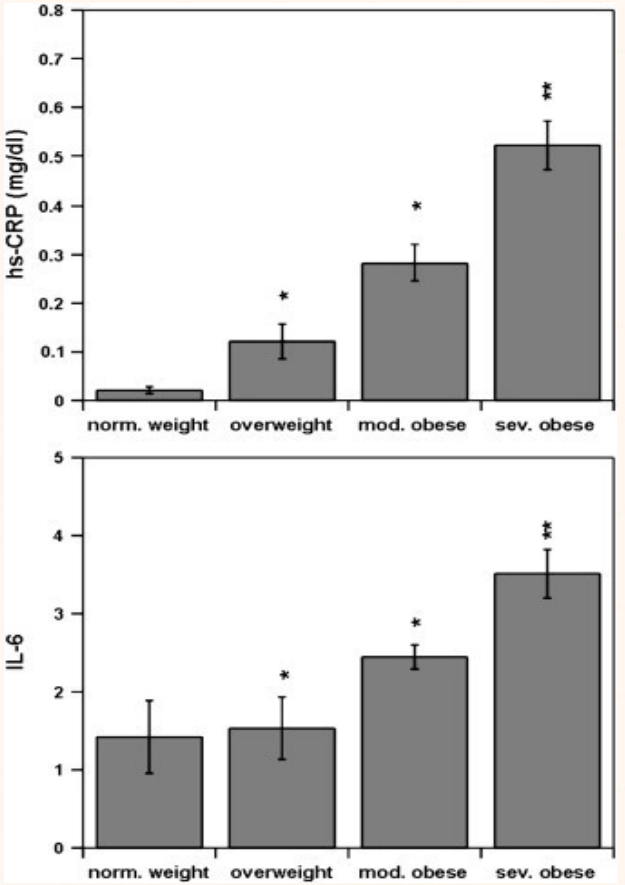



Camhi 2011

Camhi SM, et al. Prevalence of cardiometabolic risk factor clustering and body mass index in adolescents. J Pediatr. 2011 Aug;159(2):303-7.

# Obesity is a Driver for Inflammation

- 439 obese children and adolescents
- Prevalence of MetS increased directly with the degree of obesity
- Obesity may be the most important cause of insulin resistance
- Obesity directly linked to inflammation (CRP and IL-6)




D'Adamo 2011

D'Adamo E, et al. Metabolic syndrome in pediatrics: old concepts revised, new concepts discussed. Pediatr Clin North Am. 2011 Oct;58(5):1241-55, xi.
Weiss R, Dziura J, et al. Obesity and the metabolic syndrome in children and adolescents. N Engl J Med. 2004 Jun 3;350(23):2362-74.

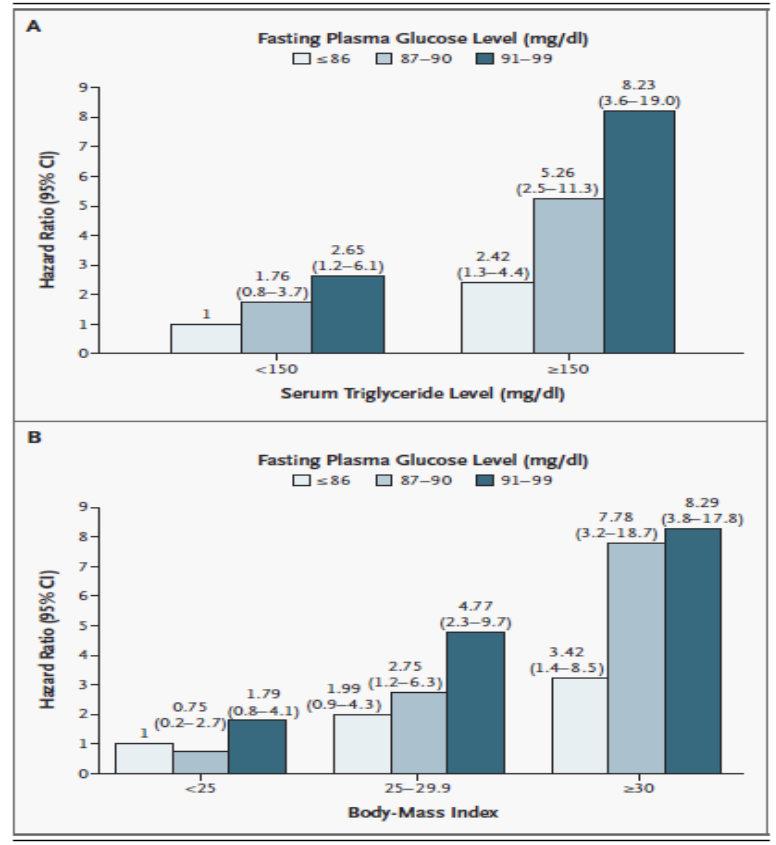
# Glucose Normal Range – Arbitrary?

- CARMA study: ~11,000 men and women with FPG < 100 mg/dL as well as 100 - 125 mg/dL, without CVD
- Fasting glucose levels in the high normal range (95-99 mg/dL) had an increased CVD risk when compared with levels < 80 mg/dL, (HR 1.53; P < .001).
- Independently increased risk of CVD with rising FPG levels in the normal range

Shaye K, et al. Fasting glucose levels within the high normal range predict cardiovascular outcome. Am Heart J. 2012 Jul;164(1):111-6.

# Normoglycemia

- Metabolic, Lifestyle, and Nutrition Assessment in Young Adults (MELANY)
- 13,163 young men with FPG less than 100 mg
- Age-adjusted hazard ratios for T2D increased across quintiles of fasting plasma glucose levels, reaching 3.05 for the top quintile as compared with the bottom quintile
- Independent of other traditional risk factors for diabetes

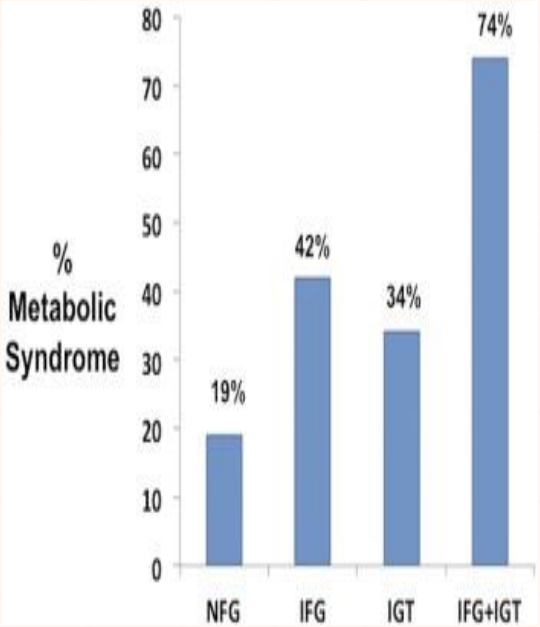



Tirosh 2005

Tirosh A, et al. Normal fasting plasma glucose levels and type 2 diabetes in young men. N Engl J Med. 2005 Oct 6;353(14):1454-62.

# Pre-diabetes – Not pre-disease

- ADA now defines pre-diabetes as IFT, IGT, or HbA1c of 5.7% to 6.4%
- By 2030, nearly 500 million worldwide predicted
- Associated with increased stroke risk, particularly when combined with impaired glucose tolerance
- Increased prevalence of Met-S, CVD
- Linked to nerve and kidney damage
- Progression to diabetes
  - 5-10% of people per year with pre-diabetes will progress to diabetes
  - 15–19% in those with both IFT and IGT

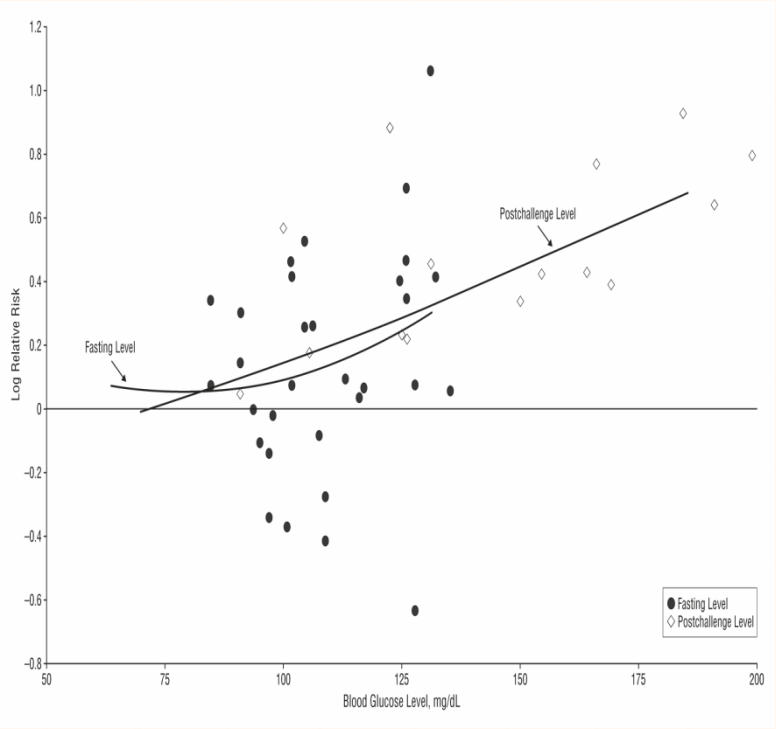



Grundy 2012

Lee M et al. Effect of pre-diabetes on future risk of stroke: meta-analysis. BMJ. 2012 Jun 7;344:e3564. doi: 10.1136/bmj.e3564.
Grundy SM. Pre-diabetes, metabolic syndrome, and cardiovascular risk. J Am Coll Cardiol. 2012 Feb 14;59(7):635-43.
Tabák AG, et al Prediabetes: a high-risk state for diabetes development. Lancet. 2012 Jun 16;379(9833):2279-90.

# Pre-diabetes and CVD Risk

- Meta-analysis of 38 prospective studies
- Highest postchallenge blood glucose level (150-194 mg/dL) had a 27% greater risk for CVD compared with the group with the lowest level (69-107 mg/dL)
- Postchallenge blood glucose level has a linear relationship with CVD risk in the non-diabetic range, perhaps leveling out at 100 mg/dL

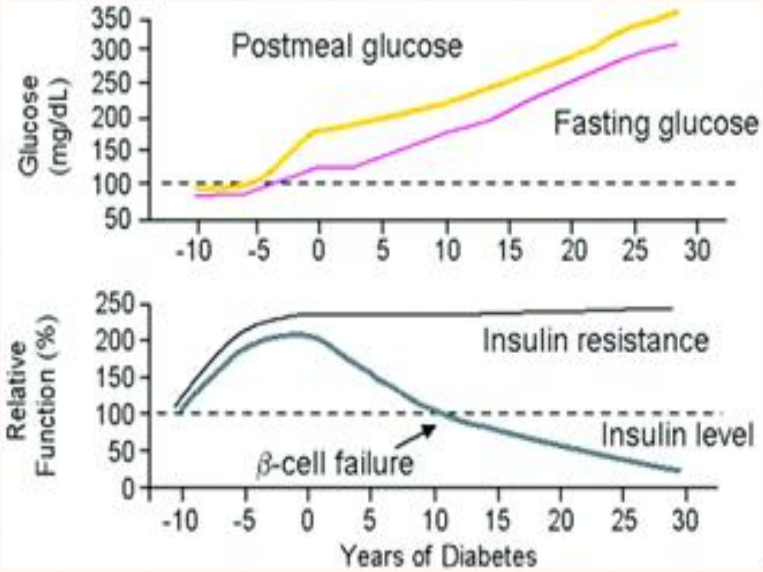



Levitan 2004

Levitan EB, et al. Is nondiabetic hyperglycemia a risk factor for cardiovascular disease? A meta-analysis of prospective studies. Arch Intern Med. 2004 Oct 25;164(19):2147-55.

# Progression to Diabetes

- While pre-diabetes does not always progress to diabetes, it is certainly on a continuum
- Diabetes is characterized by progressive worsening of glycemic control
- Insulin resistance and beta-cell failure occur early, and if allowed to progress, diabetes is end-result
- It is estimated that beta-cell function may already be reduced by 50% by the time diabetes is diagnosed

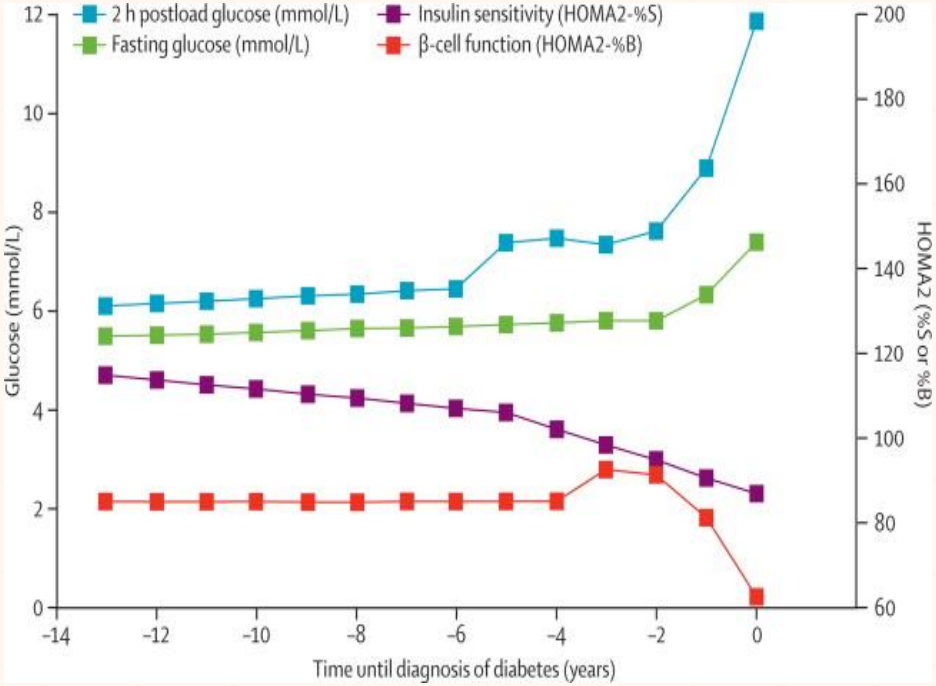



LeRoith 2002

LeRoith D. Beta-cell dysfunction and insulin resistance in type 2 diabetes: role of metabolic and genetic abnormalities. Am J Med. 2002 Oct 28;113 Suppl 6A:3S-11S

# Continuum of Disease

- While pre-diabetes may identify distinct physiological dysfunctions (i.e. IFG vs. IGT), it is not benign
- Risk is better identified using continuum, vs. using distinct categories

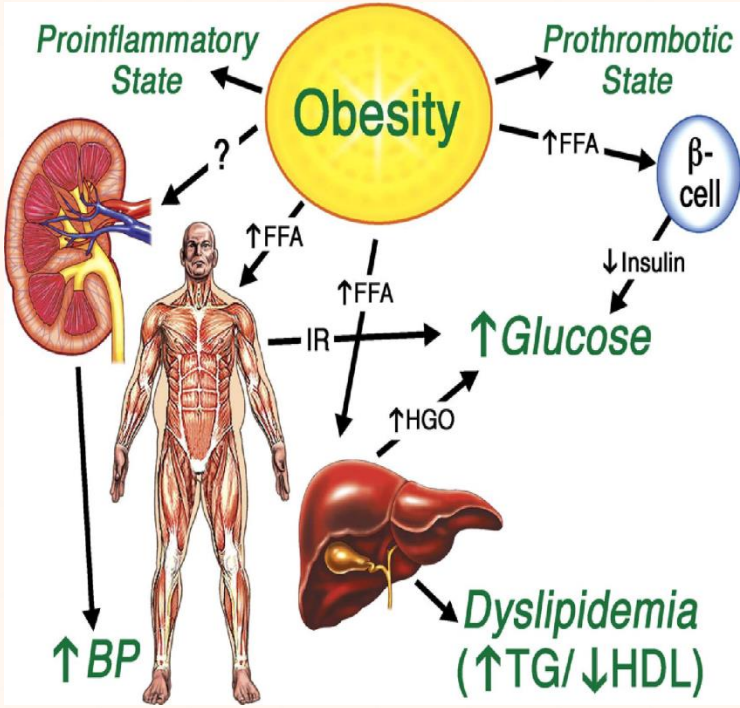



Tabák 2012

Tabák AG, et al. Prediabetes: a high-risk state for diabetes development. Lancet. 2012 Jun 16;379(9833):2279-90.

# Pathophysiology

- Two major defects:
  - Development of insulin resistance
  - Defective beta-cell function
- Hepatic insulin resistance is marked by an inappropriately high rate of hepatic glucose, despite elevated insulin concentrations
- Peripheral insulin resistance is the inability of endogenous insulin to increase plasma glucose uptake by peripheral tissues
- Insulin resistance derives from multiple factors including inflammatory pathways, toxic effects of excess lipids, mitochondrial dysfunction, ectopic fat deposition, stress hormones, lack of physical activity, etc.

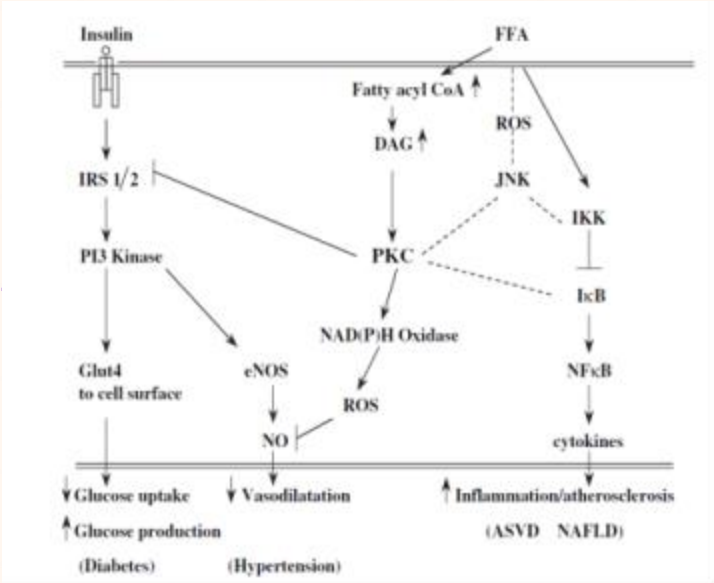



Grundy 2012

Grundy SM. Pre-diabetes, metabolic syndrome, and cardiovascular risk. J Am Coll Cardiol. 2012 Feb 14;59(7):635-43.
Fradkin JE. Confronting the urgent challenge of diabetes: an overview. Health Aff (Millwood). 2012 Jan;31(1):12-9.

# Pathophysiology

- Increased body fat a significant risk factor for insulin resistance, particularly ectopic liver fat
- Adipose tissue now recognized as an active endocrine organ key to the pathogenesis of insulin resistance through several released metabolites, hormones, and adipocytokines
  - Adiponectin strongly and inversely related to central adiposity, diabetes, impaired glucose tolerance
  - Fat also stores environmental toxins
- Non-esterified free fatty acids inhibit insulin's suppression of hepatic glucose production, and glucose uptake in peripheral cells. Additionally, an inflammatory cascade is triggered, which includes the activation of NF KappaB and inflammatory compounds
- Elevated C-reactive protein carries a 3-(nearly) 6–fold increase in risk for Met-S

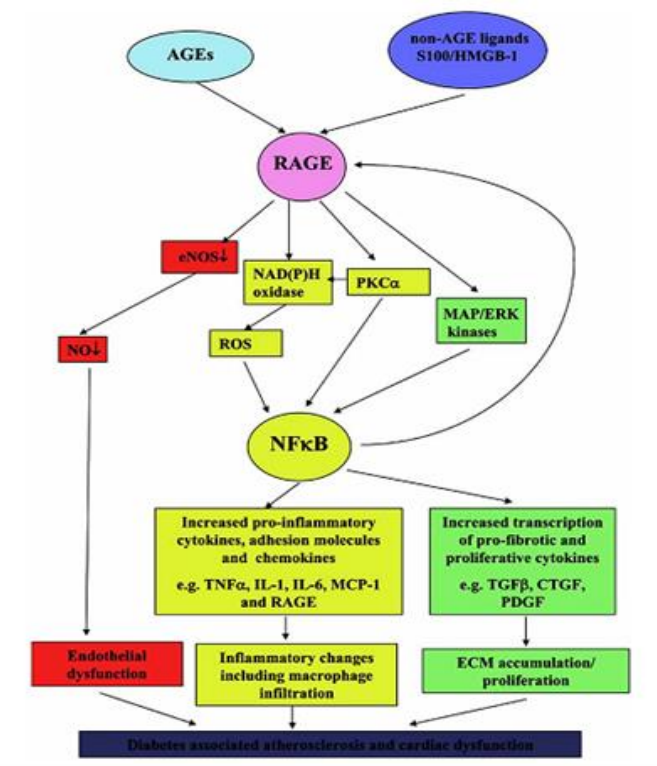




Chiarelli F, et al. Insulin Resistance and Obesity in Childhood. Eur J Endocrinol. 2008 Sep 19.
Boden G. Obesity and free fatty acids. Endocrinol Metab Clin North Am. 2008 Sep;37(3):635-46, viii-ix
Ishikawa S, et al. Metabolic syndrome and C-reactive protein in the general population: JMS Cohort Study. Circ J. 2007 Jan;71:26-31.

# AGEs-Induced Damage

- Advanced glycation end-products
  - AGEs formed by a non-enzymatic reaction between a ketone group of glucose (or aldehydes) and the amino groups of proteins, lipids, or nucleic acids
  - Abundance of glucose accelerates rate of formation and accumulation of AGEs
  - Generate ROS, inflammation, impair endothelial function, quench NO, etc.
  - Accelerate retinopathy, neurodegenerative disease, cardiovascular disease, and the aging process

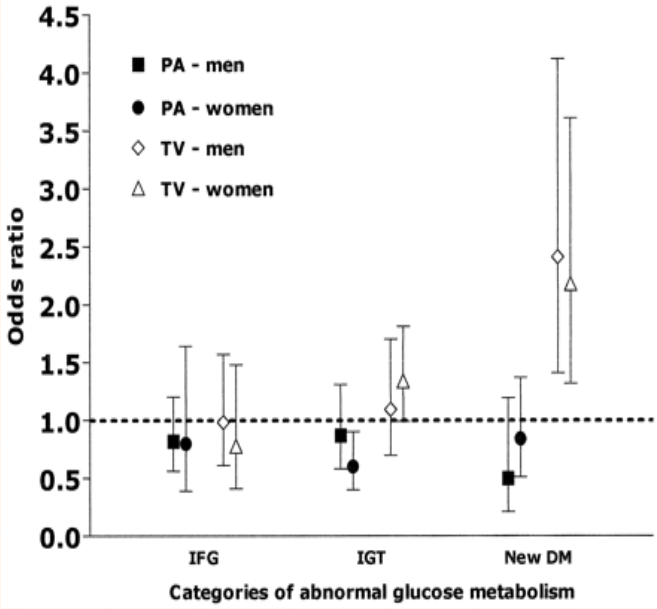



Jandeleit-Dahm 2008

Jandeleit-Dahm K, et al. The role of AGEs in cardiovascular disease. Curr Pharm Des. 2008;14(10):979-86.
Grillo MA, et al. Advanced glycation end-products (AGEs): involvement in aging and in neurodegenerative diseases. Amino Acids. 2008 Jun;35(1):29-36.

# Contributing Factors

- Sedentary lifestyle partly explains
  - 800 men over 20 years, physical inactivity and obesity were both found to be independent predictors of insulin resistance
  - Prolonged TV and computer time can more than double the risk for Met-S
  - Sedentary lifestyle has risk *independent of exercise levels* – studies of 50,000 men & 38,000 women




Dunstan 2004


Ingelsson E, et al. Relative importance and conjoint effects of obesity and physical inactivity for the development of insulin resistance. Eur J Cardiovasc Prev Rehabil. 2009 Feb;16(1):28-33

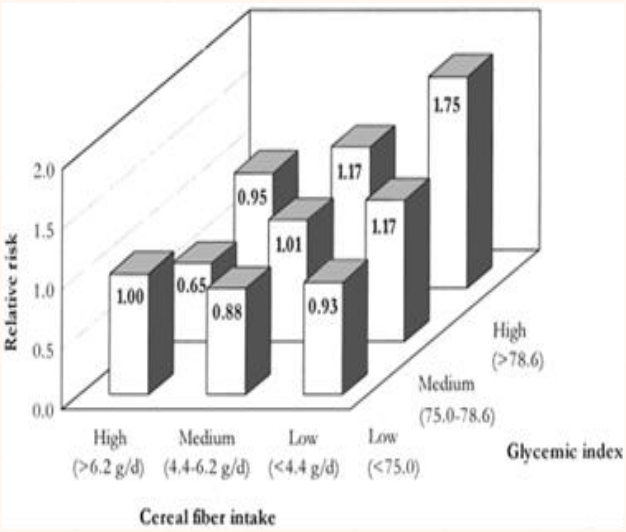
Hu FB, et al. Television watching and other sedentary behaviors in relation to risk of obesity and type 2 diabetes mellitus in women. JAMA. 2003 Apr 9;289(14):1785-91.

Hu FB, et al. Physical activity and television watching in relation to risk for type 2 diabetes mellitus in men. Arch Intern Med. 2001 Jun 25;161(12):1542-8.

Dunstan DW, et al. Physical activity and television viewing in relation to risk of undiagnosed abnormal glucose metabolism in adults. Diabetes Care. 2004 Nov;27(11):2603-9.

# Diet Has Large Role

- Refined carbohydrates and foods with a high glycemic index/load substantially increases risk
- Thirteen percent of US had added sugars intake > 25% total calories
- A low intake of fruits, vegetables, legumes, whole grain, and fiber is the dietary pattern associated with the greatest risk
- Higher fiber and cereal intake reduces risk
- Fiber viscosity may be key variable in decreasing postprandial glycemia




Schulze 2004

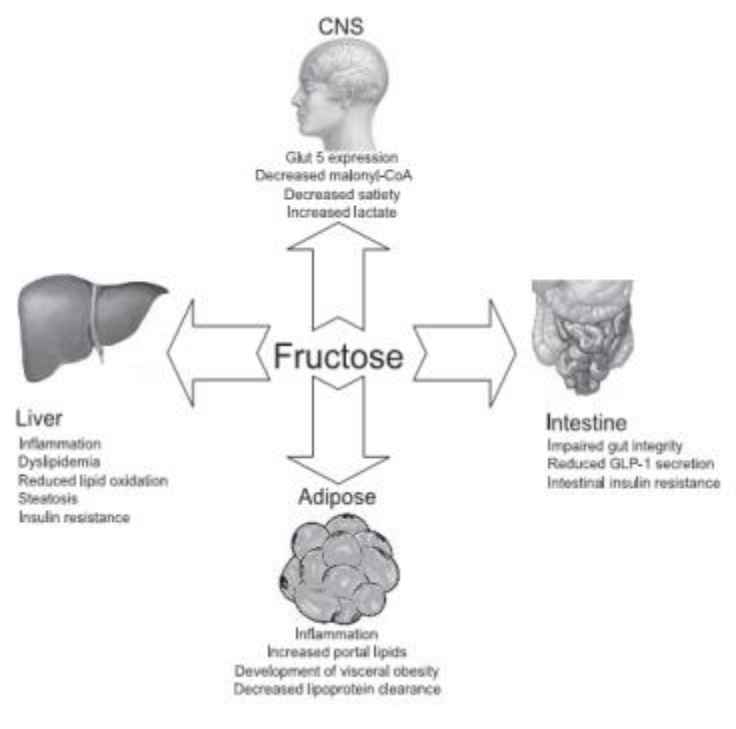

Schulze et al. Glycemic index, glycemic load, and dietary fiber intake and incidence of type 2 diabetes in younger and middle-aged women. Am J Clin Nutr. 2004 Aug;80(2):348-56.

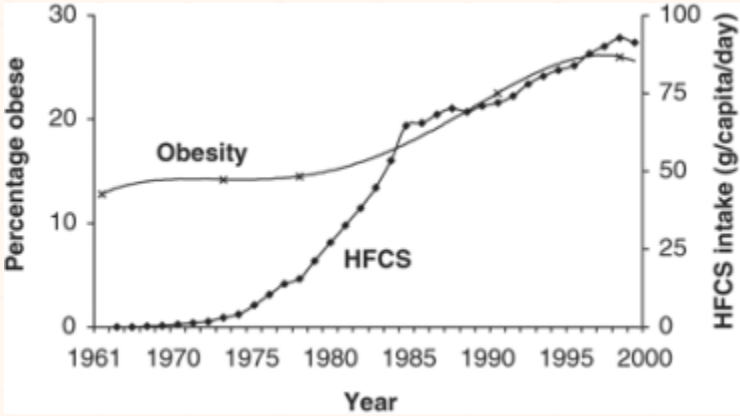
Barclay et al. Glycemic index, glycemic load, and chronic disease risk--a meta-analysis of observational studies. Am J Clin Nutr. 2008 Mar;87(3):627-37

Marriott BP, et al. Intake of added sugars and selected nutrients in the United States, National Health and Nutrition Examination Survey (NHANES) 2003-2006. Crit Rev Food Sci Nutr. 2010 Mar;50(3):228-58.

# Fructose - A Chronic Toxin?

- Increase of dietary fructose (alone, or as sucrose) has increased 1000% in 40 years, mostly as HFCS
- Fructose was 10% of caloric intake during last 10 years.
- Originally proposed as the ideal sweetener for people with diabetes
- Direct association between insulin resistance and fructose intake. Association between GL and IR may be due to fructose
- Multiple pathways for NAFLD causation, including de novo lipogenesis, mitochondrial disruption – 70% of individuals with fatty liver have Met-S

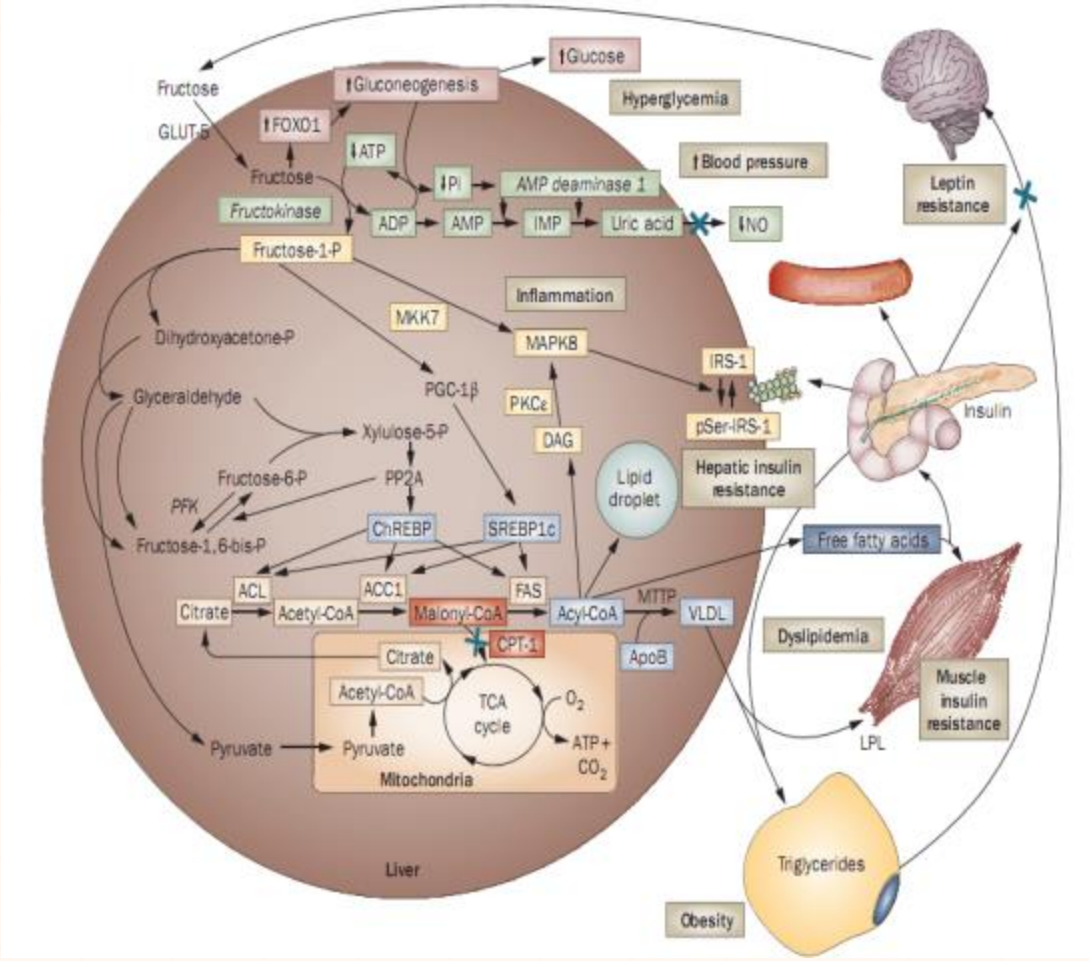



Vos MB,et al. Dietary fructose consumption among US children and adults: the Third National Health and Nutrition Examination Survey. Medscape J Med. 2008 Jul 9;10(7):160.
Association between glycemic index, glycemic load, and fructose with insulin resistance: the CDC of the Canary Islands study. Eur J Nutr. 2010 Dec;49(8):505-12.
Johnson RK, et al. Dietary sugars intake and cardiovascular health: a scientific statement from the American Heart Association. Circulation. 2009 Sep 15;120(11):1011-20.

# Mechanisms of Fructose Toxicity

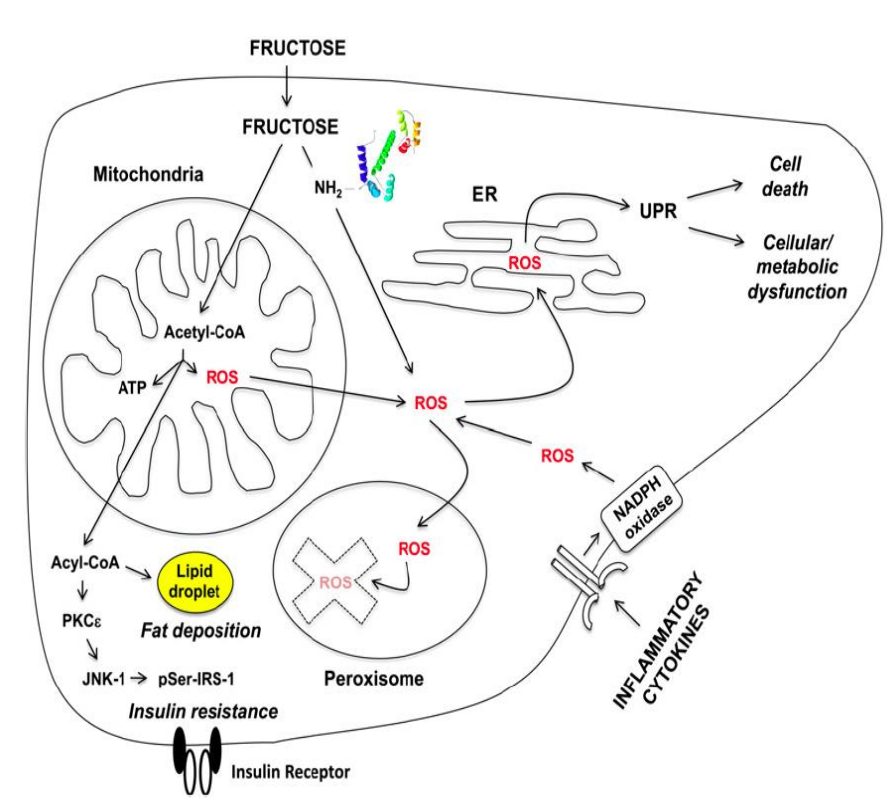
- Low fat diet with fructose/sucrose physiologically like a high fat diet
- Hepatic load is triple for fructose compared to glucose
- Causes leptin resistance (loss of appetite control), and interferes with ghrelin signaling
- Increases de novo lipogenesis (VLDL production and secretion), uric acid, and free fatty acids (peripheral and hepatic insulin resistance.
- Induces the transcription of the enzyme JNK-1, initiates inflammatory cascade




Lustig RH. Fructose: metabolic, hedonic, and societal parallels with ethanol. J Am Diet Assoc. 2010 Sep;110(9):1307-21.

# Fructose as Mitochondrial and ER Toxin

- Fructose drives ROS production, causing mitochondrial dysfunction, and endoplasmic reticulum stress -> unfolded protein response -> Cellular dysfunction/death
- Nonenzymatic fructosylation: 7 times more rapid than protein
- Fructose generates 100 times more ROS than glucose
- Shares mechanisms with trans-fats, branched-chain amino acids, and ethanol



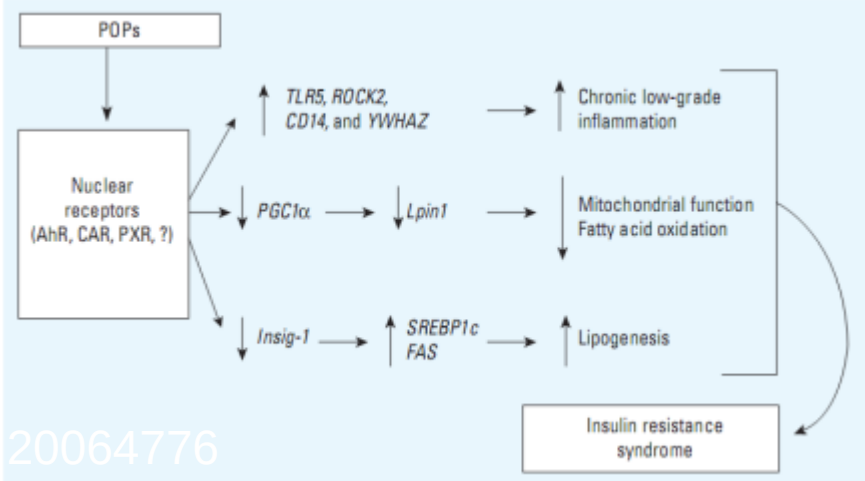

Bremer 2012



Bremer AA, et al. Toward a unifying hypothesis of metabolic syndrome. Pediatrics. 2012 Mar;129(3):557-70.

# Environmental Toxins

- 38-fold risk for diabetes in those with highest levels of 6 POPS (NHANES).
- In people with undetectable levels of POPs, the typically robust association between obesity and diabetes was not observed. i.e. when POPs concentrations were very low, prevalent type 2 diabetes was rare even among obese persons
- Prospective cohort studies have found increased risk of diabetes, modified glucose metabolism, or insulin resistance
- Arsenic: OR of 3.58 for T2D, comparing 80th vs 20th percentiles (NHANES)





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Lee DH, et al. Low dose of some persistent organic pollutants predicts type 2 diabetes: a nested case-control study. Environ Health Perspect. 2010 Sep;118(9):1235-42.

Navas-Acien A, et al. Arsenic exposure and prevalence of type 2 diabetes in US adults. JAMA. 2008 Aug 20;300(7):814-22.

# POPs: Widespread Low Dose Exposure

- Now more than 80,000 different chemicals in commerce
- 49 POPs measured by NHANES study – at least 20 found in >60% of US pop, some found in >80%
  - Hexachlorobenzene found in 0.6%; DDE found in nearly all
- Canadian study found 46 of 69 POPs measured
- BPA in 95%, phthalates in 75% of urine samples in US

Landrigan et al. Children's vulnerability to toxic chemicals: a challenge and opportunity to strengthen health and environmental policy. Health Aff (Millwood). 2011;30(5):842-850
Ha MH, et al. Association between serum concentrations of persistent organic pollutants and self-reported cardiovascular disease prevalence: results from the National Health and Nutrition Examination Survey, 1999-2002. Environ Health Perspect. 2007 Aug;115(8):1204-9.
Colacino JA, et al. Dietary intake is associated with phthalate body burden in a nationally representative sample. Environ Health Perspect. 2010 Jul;118(7):998-1003.

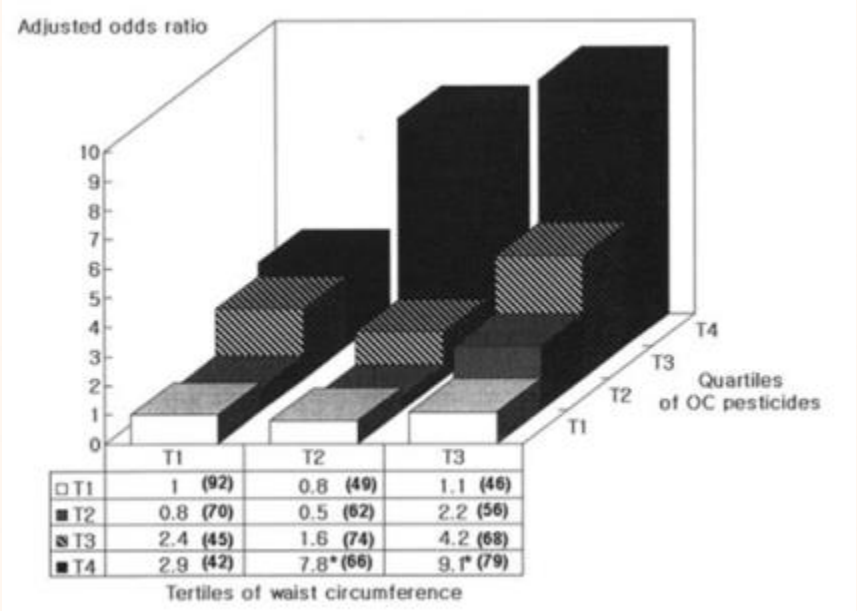
# Physiological Effects of POPs

- Diverse mechanisms, due to various chemical structures of POPs:
  - Endocrine disruption
  - Blood sugar regulation dysruption (interference/mimic insulin,)
  - Mitochondrial damage
  - Inflammatory cytokines
  - Alterations in aryl hydrocarbon nuclear receptor translocator
  - Peroxisome proliferator activated receptor (PPAR) agonist
  - Stimulation of tumor necrosis factor-α expression
  - Intrauterine and/or epigenetic and trans-generational effects.
    - For example, higher cord blood levels of hexachlorobenzene associated with 2x greater risk for obesity in children

Smink A, et al. (2008) Exposure to hexachlorobenzene during pregnancy increases the risk of overweight in children aged 6 years. Acta Paediatr 97, 1465–1469.

# Persistent Organic Pollutants

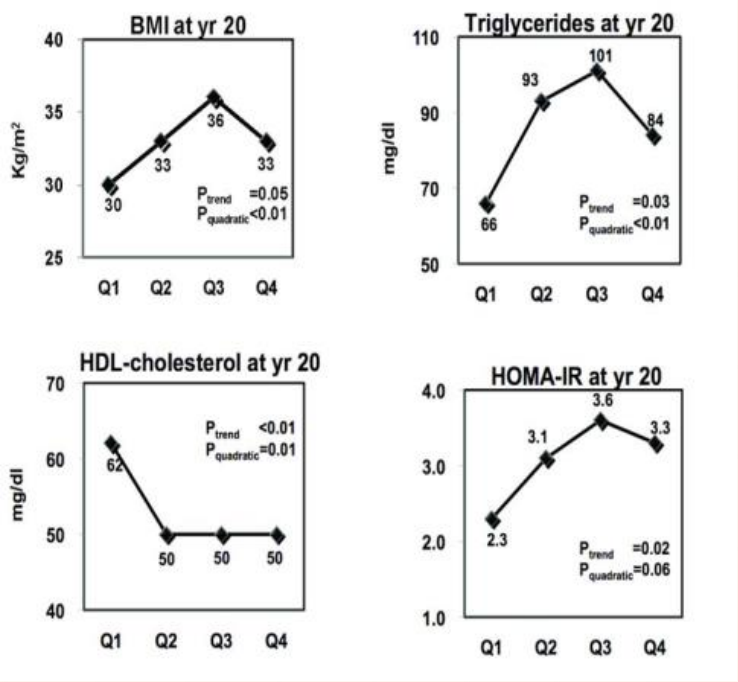
- Among 5 POPs subclasses, organochlorine (OC) pesticides were most strongly and consistently associated with metabolic syndrome: adjusted odds ratios (ORs) of 1.0, 1.5, 2.3 and 5.3 across OC pesticide quartiles
- Data suggests that adipose storage of toxins may be most significant role of obesity in diabetes epidemic




Lee DH, et al. Association between serum concentrations of persistent organic pollutants and insulin resistance among nondiabetic adults: results from the National Health and Nutrition Examination Survey 1999-2002. Diabetes Care. 2007 Mar;30(3):622-8

# POPs - Diabetes

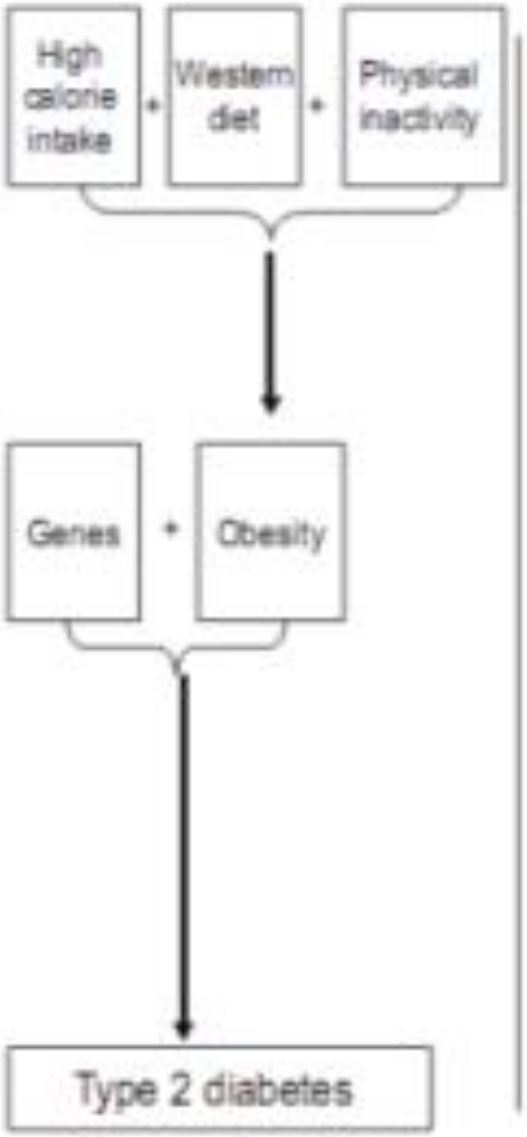
- OC pesticides and PCBs cause insulin resistance and altered metabolism in very early stages, before diabetes and obesity.
- Low dose POPs “are likely involved in all steps of pathogenesis of type 2 diabetes, even including the development of obesity”
- Different POPs cause different dysfunctions, which may be why metabolic alterations of diabetes occur together
  - e.g. p,p'-DDE influences development of pre-diabetic conditions, while trans-nonachlor influences progression from pre-diabetes to diabetes.
- U-Shaped responses (see figure for p,p'-DDE)



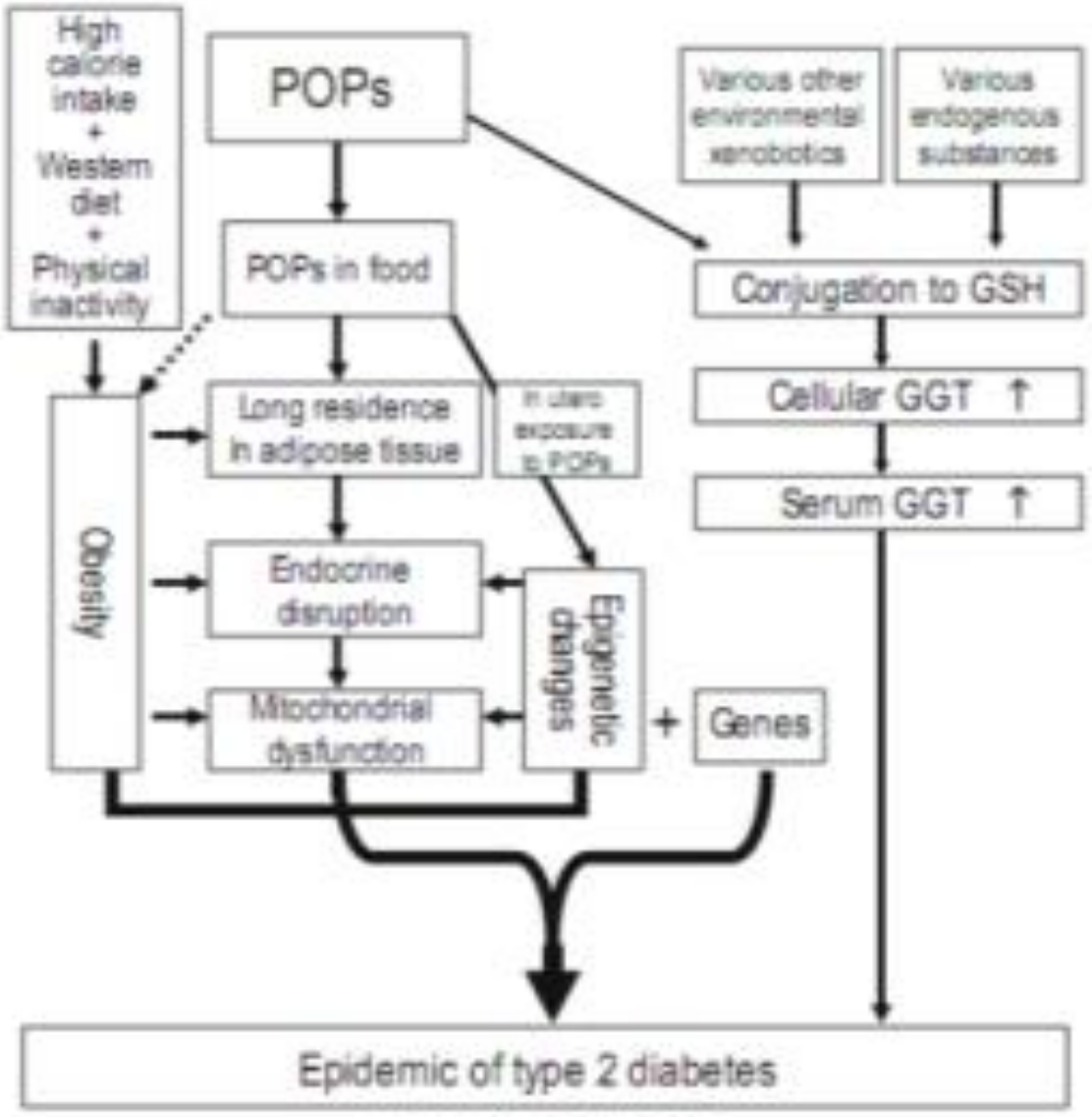

Lee 2011

Lee DH, et al. Low dose organochlorine pesticides and polychlorinated biphenyls predict obesity, dyslipidemia, and insulin resistance among people free of diabetes. PLoS One. 2011 Jan 26;6(1):e15977.

# New (Old!) Disease Paradigm



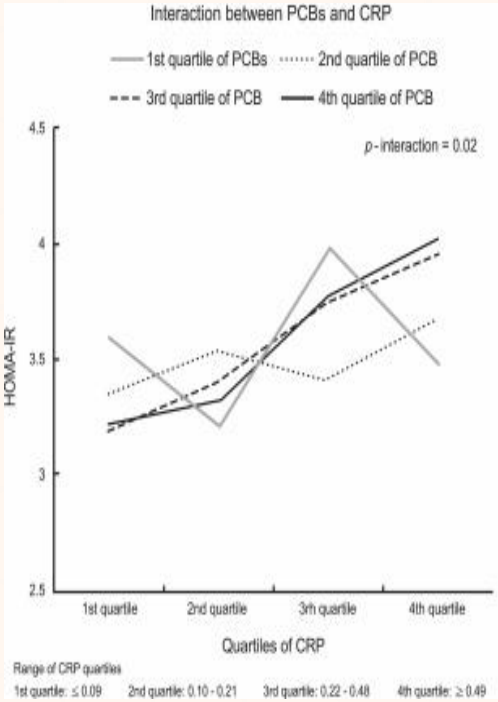

Current paradigm

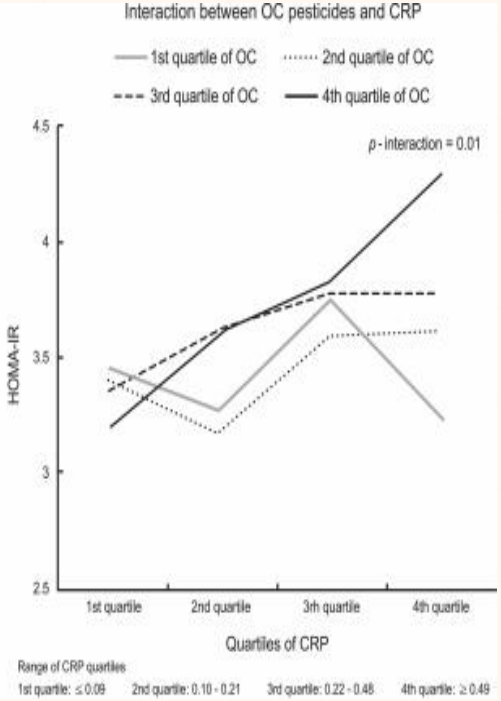



New hypothesis

# POPs - Inflammation and Insulin Resistance

- OC pesticides positively associated with CRP among US with background exposure levels
- CRP was NOT associated with HOMA-IR among those with low serum OC pesticides or PCBs
- CRP was STRONGLY associated with HOMA-IR in the presence of high serum concentrations



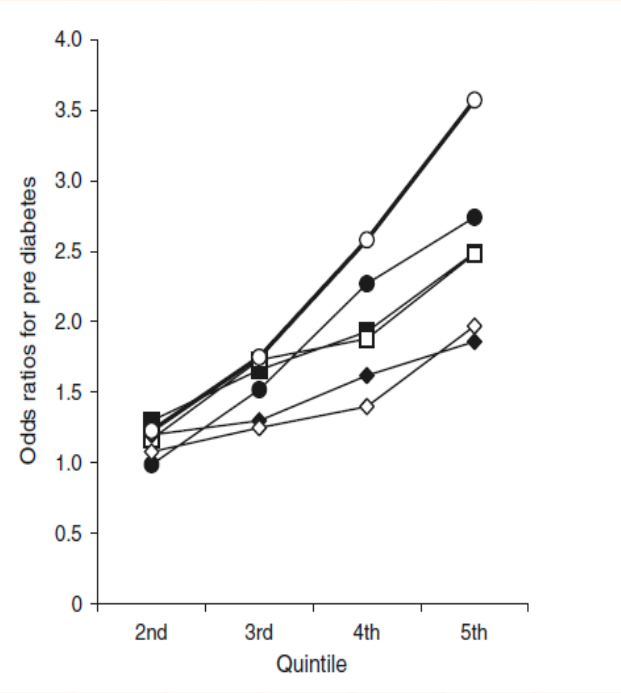




Kim 2012

Kim KS, et al. Interaction Between Persistent Organic Pollutants and C-reactive Protein in Estimating Insulin Resistance Among Non-diabetic Adults. J Prev Med Public Health. 2012 Mar;45(2):62-9.

# POPs – Pre-diabetes

- Over 1200 participants, fasting glucose and OGTT performed, with serum levels of 5 POPs
- All individual POPs tested were associated with progressive increase in prevalence of pre-diabetes
- More than triple prevalence of pre-diabetes seen in those in the 5$^{th}$ quartile, with a synergistic effect from 5 POPs

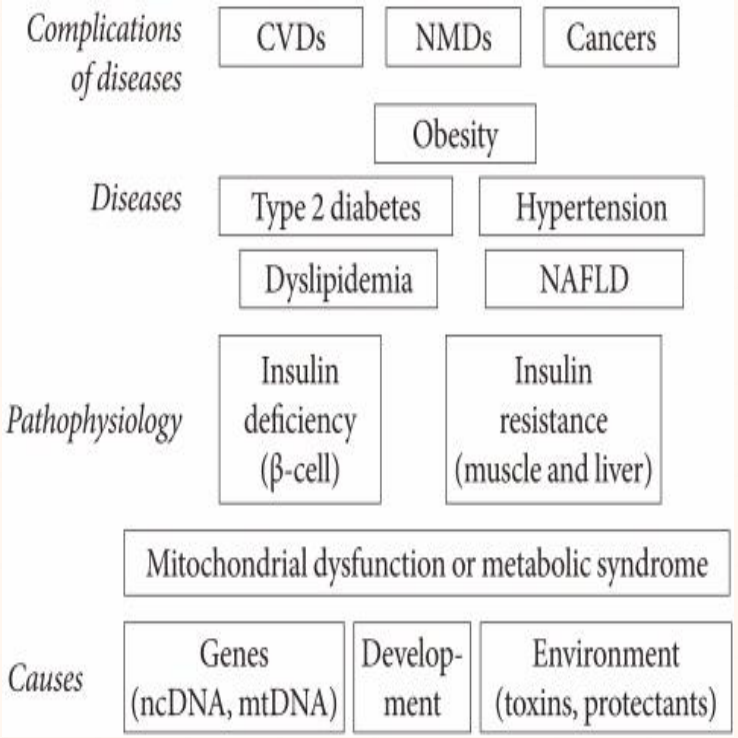



Ukropec 2010

Ukropec J, et al. High prevalence of prediabetes and diabetes in a population exposed to high levels of an organochlorine cocktail. Diabetologia. 2010 May;53(5):899-906.

# POPs: Also Mitochondrial Inhibitors

- Mitochondrial theory of metabolic syndrome
- Atrazine, for example, has been widely used in US since 1960's, and inhibits photosynthesis and mitochondrial function
- Animal models show both mitochondrial inhibition and insulin resistance
- Overlap between obesity rates and areas of heavy use




Lee 2011


Lim S, et al. Chronic exposure to the herbicide, atrazine, causes mitochondrial dysfunction and insulin resistance. PLoS One. 2009;4(4):e5186.

Lee HK. Mitochondrial dysfunction and insulin resistance: the contribution of dioxin-like substances. Diabetes Metab J. 2011 Jun;35(3):207-15.

# Obesogens

- Gaining acceptance as a cause of increased weight via a variety of mechanisms:
  - Increasing the number of fat cells (and fat storage into existing fat cells)
  - Decreasing the amount of calories burned at rest
  - Altering energy balance to favour storage of calories
  - Influencing the mechanisms through which the body regulates appetite and satiety
- Recent review of 24 original studies on humans, relating EDCs (Endocrine Disrupting Chemicals) to body size
  - Prenatal PCB, DDE, and HCB exposure associated with subsequent obesity
  - Evidence of dose effect for some chemicals (PCB, DDE, phthalates): weight gain at lower doses and weight loss at higher doses.
  - A gender effect was found for the association between PCB exposure and obesity: girls being more susceptible

Tang-Péronard JL et al. Endocrine-disrupting chemicals and obesity development in humans: a review. Obes Rev. 2011 Aug;12(8):622-36. doi: 10.1111/j.1467-789X.2011.00871.x.

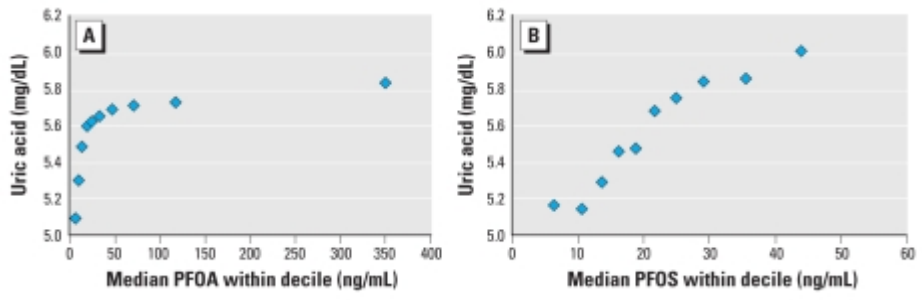
# Phthalates - Body Size and Fat Distribution

- PIVUS population
  - 4 phthalate metabolites detectable in serum of 96% of population
  - In women, MiBP associated with increased fat amount in the subcutaneous abdominal region, measured 2 yrs later
- New York City children
  - Dose response relationship between phthalate metabolites and body mass index and waist circumference
- Associated with both diabetes prevalence as well as insulin secretion & resistance

Lind PM, et al. Serum concentrations of phthalate metabolites related to abdominal fat distribution two years later in elderly women. Environ Health. 2012 Apr 2;11(1):21.
Teitelbaum SL, et al. Associations between phthalate metabolite urinary concentrations and body size measures in New York City children. Environ Res. 2012 Jan;112:186-93.
Lind PM, et al. Circulating Levels of Phthalate Metabolites Are Associated With Prevalent Diabetes in the Elderly. Diabetes Care. 2012 Apr 12.

# PFCs - Metabolic Abnormalities

- PFNA associated with impaired β-cell function and clinical hyperglycemia
- PFOS independently associated with increases in both blood insulin and insulin resistance status (HOMA-IR), but positively associated with β-cell function (thus no net affect on glucose)
- PFOA and PFOS associated with increased serum uric acid



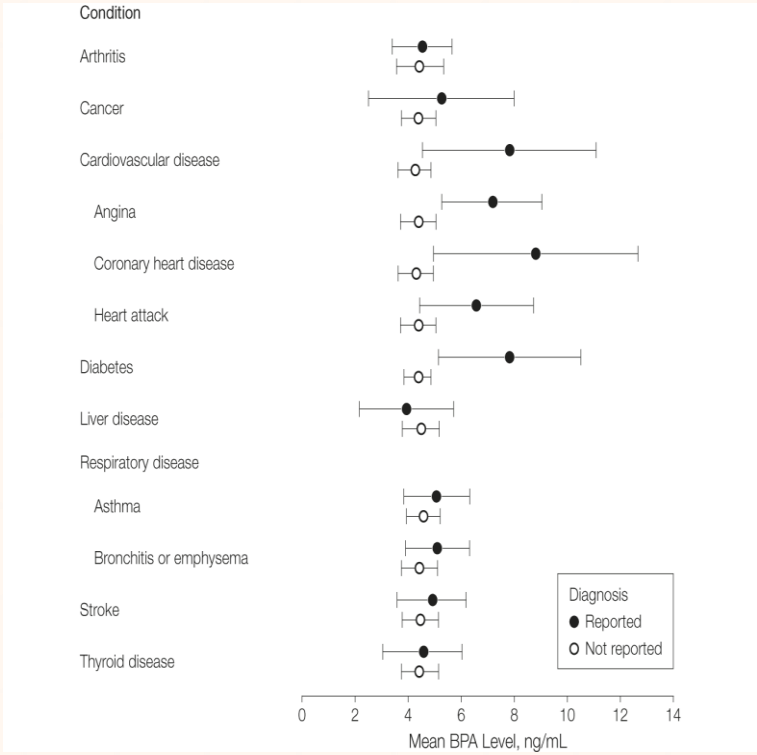

Steenland 2010


Lin CY, et al. Association among serum perfluoroalkyl chemicals, glucose homeostasis, and metabolic syndrome in adolescents and adults. Diabetes Care. 2009 Apr;32(4):702-7.

Steenland K et al. Association of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) with uric acid among adults with elevated community exposure to PFOA. Environ Health Perspect. 2010 Feb;118(2):229-33.

# Bisphenol A

- NHANES 2003-2004: Urinary BPA associated with increased diabetes risk (OR per 1-SD increase in BPA concentration, 1.39) and GGT levels
- NHANES 2003/04 and 2005/06: BPA linked to both obesity and central obesity (roughly 2-fold risk)




Lang 2008

Lang IA, et al. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. JAMA. 2008 Sep 17;300(11):1303-10.
Carwile JL, et al. Urinary bisphenol A and obesity: NHANES 2003-2006. Environ Res. 2011 Aug;111(6):825-30.

# Vitamin D & Dysglycemia

- NHANES 2003-2004
  - OR for Met-S in the highest quintile of serum 25(OH)D compared with lowest was 0.27
  - Low vitamin D also associated with diabetic neuropathy, even after controlling for multiple variables (in NHANES 01-04)
- Prospective trial
  - Baseline levels predict future insulin resistance and hyperglycemia
- 2011 systematic review
  - Those with highest levels (>25 ng/ml) had 43% lower risk of T2D than those with lowest
- Receptor Polymorphisms
  - BsmI influences BMI
  - FokI affects insulin sensitivity and serum HDL levels

Reis JP, et al. Relation of 25-hydroxyvitamin D and parathyroid hormone levels with metabolic syndrome among US adults. Eur J Endocrinol. 2008 Jul;159(1):41-8.
Filus A, et al. Relationship between vitamin D receptor BsmI and FokI polymorphisms and anthropometric and biochemical parameters describing metabolic syndrome. Aging Male. 2008 Sep;11(3):134-9.
Soderstrom LH, et al. Association between vitamin D and diabetic neuropathy in a nationally representative sample: results from 2001-2004 NHANES. Diabet Med. 2012 Jan;29(1):50-5. doi: 10.1111/j.1464-5491.2011.03379.x.
Mitri J, et al. Vitamin D and type 2 diabetes: a systematic review. Eur J Clin Nutr. 2011 Sep;65(9):1005-15. doi: 10.1038/ejcn.2011.118.

# Vitamin D

- Vitamin D associated with lower circulating adiponectin in subjects with abnormal glucose tolerance - *independently of adiposity*
- Low vitamin D also a risk factor for type 1 diabetes, and observational studies suggest supplementation reduces risk ~30% -
  - Higher doses likely have greater benefit (dose of 2000 IU had RR of 0.22)
  - Timing important (when given at 7-12 months, greatest reduction in risk)

Nimitphong H, et al. The association between vitamin D status and circulating adiponectin independent of adiposity in subjects with abnormal glucose tolerance. Endocrine. 2009 Oct;36(2):205-10.
Zipitis CS, et al. Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis. Arch Dis Child. 2008 Jun;93(6):512-7.

# Genetic Influence

- Much progress made in determining genetic basis of T2D through genomic analysis, with most associated loci pointing to primary defects in the β cell
  - Still, only roughly 10% of the heritability can be accounted for by genetic variants
- Recent genome-wide approach identified new variants associated with insulin resistance

Billings LK, et al. The genetics of type 2 diabetes: what have we learned from GWAS? Ann N Y Acad Sci. 2010 Nov;1212:59-77.
Manning AK, et al. A genome-wide approach accounting for body mass index identifies genetic variants influencing fasting glycemic traits and insulin resistance. Nat Genet. 2012 May 13;44(6):659-69. doi: 10.1038/ng.2274.

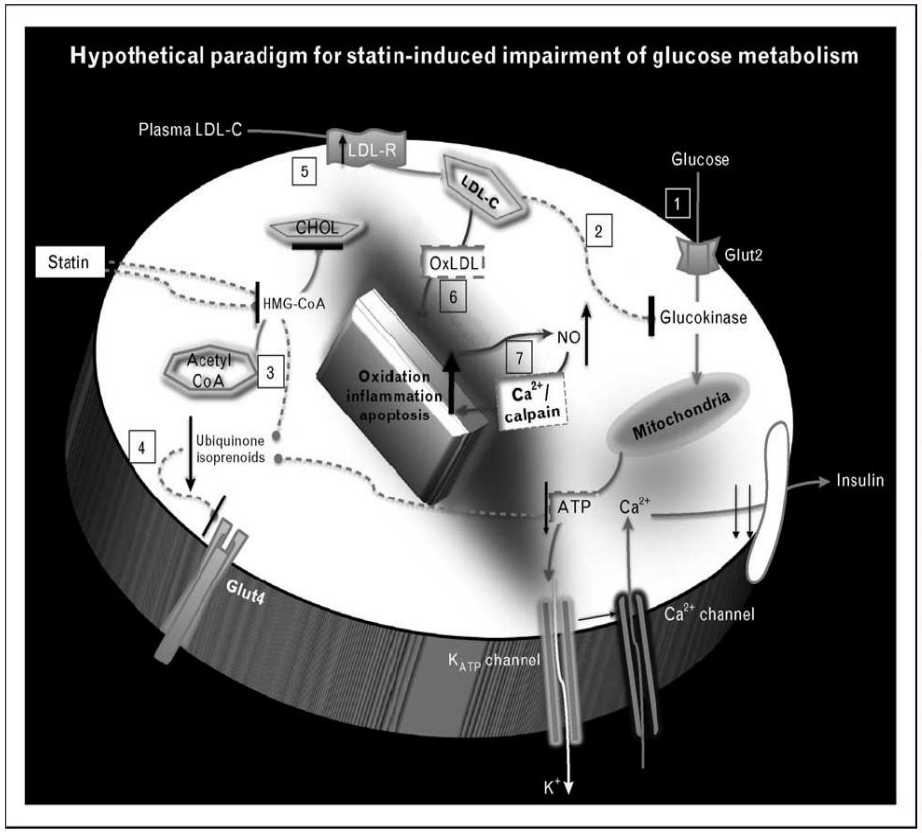
# Polymorphisms

- Many polymorphisms influence risk, and interact with dietary intake
  - AdipoQ gene and MUFAs interact to determine insulin resistance
  - Toll-like 4 interaction with saturated fat
  - Apolipoprotein E gene promoter polymorphism & dietary fat
  - Hepatic lipase gene promoter interacts with MUFA consumption
  - Others include FTO, CAPN10, PPARG, KCNJ11, and TCF7L2

Pérez-Martínez P, et al. Adiponectin gene variants are associated with insulin sensitivity in response to dietary fat consumption in Caucasian men. J Nutr. 2008 Sep;138(9):1609-14.
Cuda C, et al. Polymorphisms in Toll-like receptor 4 are associated with factors of the metabolic syndrome and modify the association between dietary saturated fat and fasting high-density lipoprotein cholesterol. Metabolism. 2011 Feb 7.
Moreno JA, et al. The apolipoprotein E gene promoter (-219G/T) polymorphism determines insulin sensitivity in response to dietary fat in healthy young adults. J Nutr. 2005 Nov;135(11):2535-40.
Gómez P, et al. The -514 C/T polymorphism in the hepatic lipase gene promoter is associated with insulin sensitivity in a healthy young population. J Mol Endocrinol. 2005 Apr;34(2):331-8.

# Drug Induced?

- Drugs which target related pathways may contribute
  - Ex: Statins
  - JUPITER and 2 meta-analyses found 9-13% increased risk for incident diabetes associated with statin therapy
  - Intensive dosing associated with greater risk
  - Those age 65+ more susceptible
  - Block CoQ10 synthesis, induce b-cell dysfunction



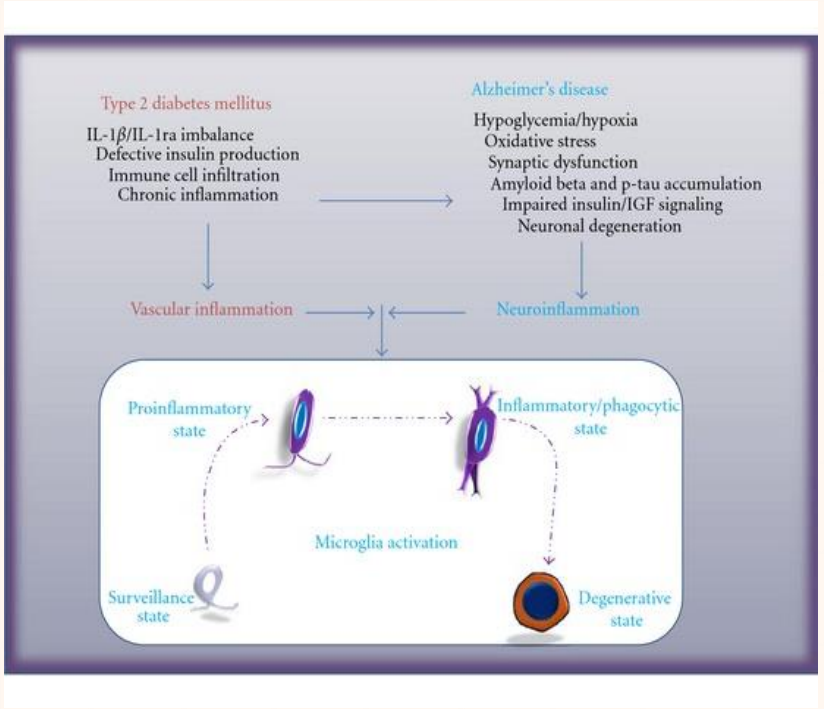

Sampson 2011


Sampson UK, et al. Are statins diabetogenic? Curr Opin Cardiol. 2011 Jul;26(4):342-7.

Preiss D, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA. 2011 Jun 22;305(24):2556-64.

# Clinical Concerns

- Alzheimer's disease/Cognitive function
  - T2D associated with increased risk for dementia and Alzheimer's disease up to 2x
  - Multiple mechanisms: insulin resistance, glucose toxicity, advanced glycation endproducts (AGEs), cerebrovascular injury, vascular inflammation, and others
  - "Cerebral insulin resistance" - increasing insulin levels do not increase neuronal activity in obese individuals compared to lean
  - Glucose excursion linked to poorer cognitive function among diabetics




Lue 2012


Lue LF, et al. Is There Inflammatory Synergy in Type II Diabetes Mellitus and Alzheimer's Disease? Int J Alzheimers Dis. 2012;2012:918680.

Kullmann S, et al. The obese brain: association of body mass index and insulin sensitivity with resting state network functional connectivity. Hum Brain Mapp. 2012 May;33(5):1052-61. doi: 10.1002/hbm.21268.

Zhong Y, et al. The relationship between glucose excursion and cognitive function in aged type 2 diabetes patients. Biomed Environ Sci. 2012 Feb;25(1):1-7.

# Additional Clinical Concerns

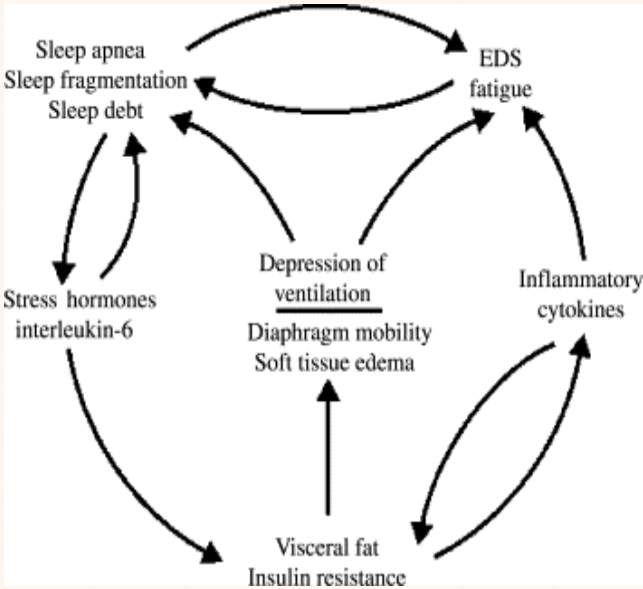
- Cardiovascular disease
  - Heart disease was noted on 68% of diabetes-related death certificates among people aged 65 years or older
  - Risk of stroke 2-4x higher
  - Heart disease death rates about 2-4 times higher
  - 2/3 of diabetics are hypertensive
- Retinopathy, Neuropathy, Nephropathy
  - T2D leading cause of blindness among adults aged 20–74 years
  - 28.5% have retinopathy
  - T2D leading cause of kidney failure (44% of new cases)
  - 60% to 70% of people with diabetes have mild to severe neuropathy
- Periodontal disease
  - 2x more likely
  - A1c > 9% 2.9x more likely to have severe periodontitis



http://www.cdc.gov/diabetes/pubs/estimates11.htm#1

# Additional Clinical Concerns

- Sleep apnea
  - Met-S and obesity (through insulin resistance and inflammation) thought to play a direct role
- Depression
  - Diabetics 2x as likely to have, and those with depression more likely to develop diabetes
- Mitochondrial Dysfunction & Inflammation
  - Mitochondrial impairment even in children of diabetics
  - Decreased capacity observed in insulin-responsive tissues, such as skeletal muscle, liver and heart




Vgontzas AN, 2005

Vgontzas AN, et al. Sleep apnea is a manifestation of the metabolic syndrome. Sleep Med Rev. 2005 Jun;9(3):211-24.
Vgontzas AN. Does obesity play a major role in the pathogenesis of sleep apnoea and its associated manifestations via inflammation, visceral adiposity, and insulin resistance? Arch Physiol Biochem. 2008 Oct;114(4):211-23.
Petersen KF, et al. Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. N Engl J Med. 2004 Feb 12;350(7):664-71

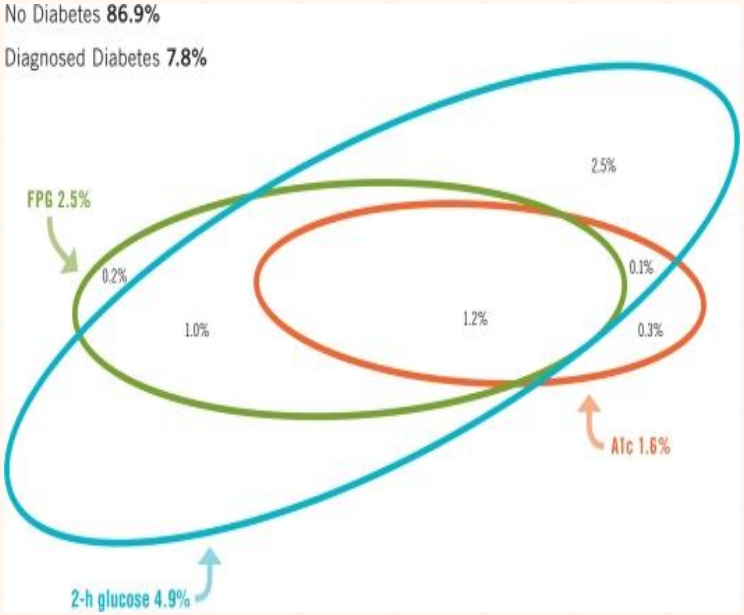
# Assessment

- Met-S
  - Diagnosis of Met-S is based on central obesity, dyslipidemia, insulin resistance, and hypertension, though the criteria vary to some degree from one organization to another
- Insulin resistance
  - In clinical practice done by oral glucose tolerance test, mathematical models such as the homeostasis model assessment (HOMA) or quantitative insulin sensitivity check index (QUICKI)
  - Downside: QUICKI and HOMA based on fasting glucose and insulin levels, thus more reflective of hepatic insulin resistance, which occurs later, than they are for peripheral or skeletal muscle insulin resistance
  - Impaired glucose tolerance (IGT) is more likely to indicate insulin resistance, while impaired fasting glucose (IFG) is more indicative of basal insulin secretion deficiency
  - Serum adiponectin has emerged as a potentially excellent marker for insulin sensitivity, though it has not yet been fully evaluated

Muniyappa R, et al. Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. Am J Physiol Endocrinol Metab. 2008 Jan;294(1):E15-26.
Faerch K, et al. Impaired fasting glycaemia vs impaired glucose tolerance: similar impairment of pancreatic alpha and beta cell function but differential roles of incretin hormones and insulin action. Diabetologia. 2008 May;51(5):853-61.

# Assessment

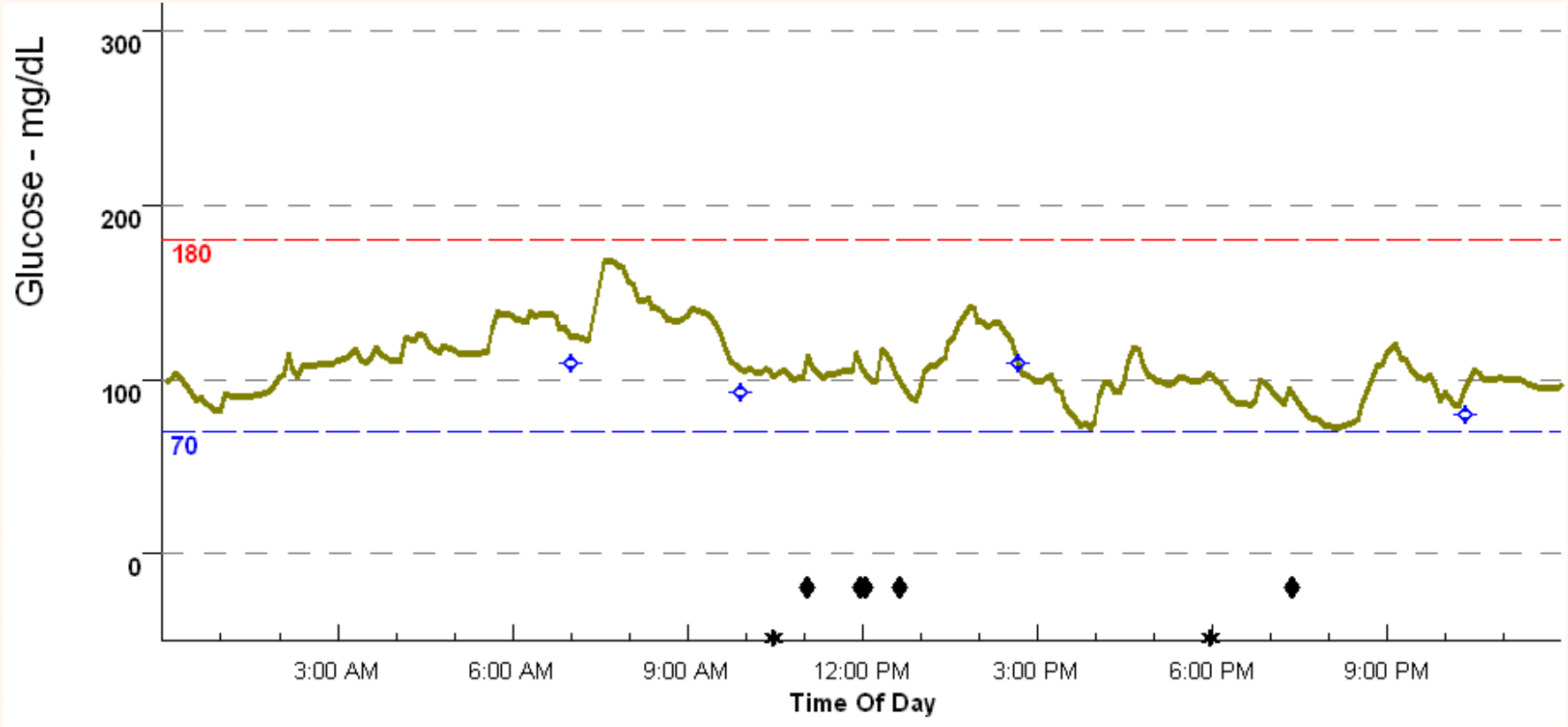
- Fasting glucose alone? Misses 30% of T2D cases
- If plasma glucose returns to baseline at one hour following glucose challenge, less insulin resistance, and lower chance of progression to diabetes (even among those with IFG)
- As HbA(1c) increases >6.0%, decrease in insulin sensitivity and β-cell function
- Subjects with impaired fasting glucose or impaired glucose tolerance have a marked decrease in β-cell function independent of their HbA(1c) level




Cowie 2010
(20067953)

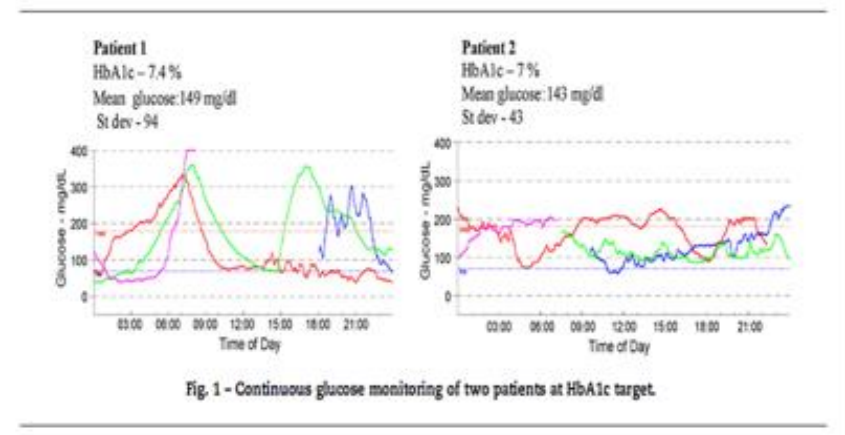

Aroda VR, et al. Approach to the patient with prediabetes. J Clin Endocrinol Metab. 2008 Sep;93(9):3259-65.
Abdul-Ghani MA, et al. The shape of plasma glucose concentration curve during OGTT predicts future risk of type 2 diabetes. Diabetes Metab Res Rev. 2010 May;26(4):280-6.
Kanat M, et The Relationship Between {beta}-Cell Function and Glycated Hemoglobin: Results from the Veterans Administration Genetic Epidemiology Study. Diabetes Care. 2011 Apr;34(4):1006-10.

# 24-Hour Blood Sugar Monitor



# Hemoglobin A1c

- Now approved for diabetes diagnosis (levels 6.5+)
- ADA's primary target for glycemic control, because it reflects serum glucose average
- However, misses daily fluctuations such as postprandial hyperglycemia, which can be detected with continuous glucose monitoring

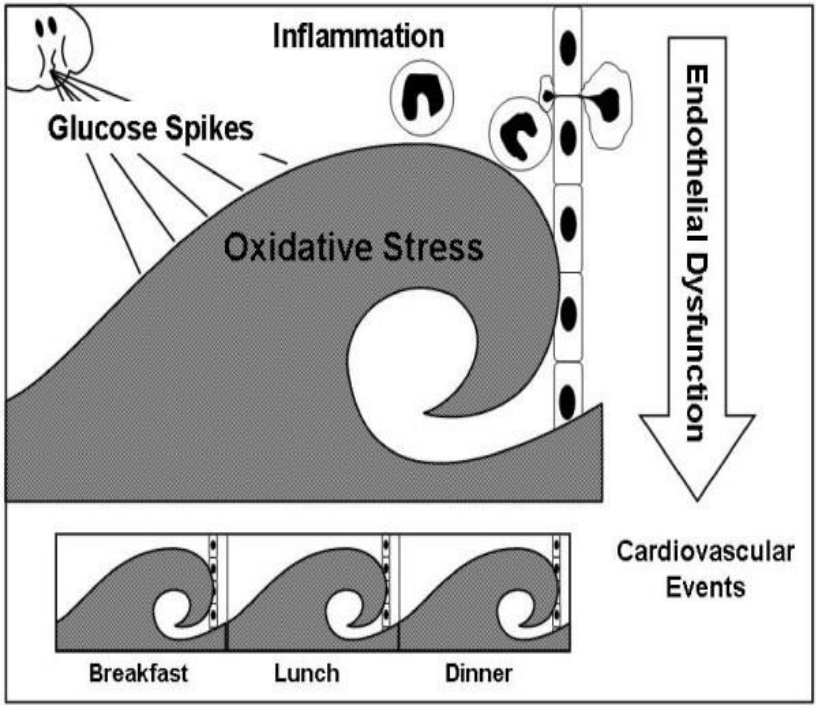



Harman-Boehm 2008

Executive summary: standards of medical care in diabetes--2011. Diabetes Care. 2011 Jan;34 Suppl 1:S4-10
Hoeks LB, et al. Real-time continuous glucose monitoring system for treatment of diabetes: a systematic review. Diabet Med. 2011 Apr;28(4):386-94.
Harman-Boehm I. Continuous glucose monitoring in type 2 diabetes. Diabetes Res Clin Pract. 2008 Dec 15;82 Suppl 2:S118-21

# Postprandial Hyperglycemia

- A greater risk factor for morbidity and mortality in type 2 diabetes and for the development of cardiovascular disease than fasting glucose
- Reductions in HbA1c do not necessarily indicate a reduction in postprandial hyperglycemia (may explain lack of benefit sometimes seen with HbA1c reduction)
- Suggests role for continuous glucose monitoring – associated with better glucose control, and detects postprandial hyperglycemia




Node 2009 (19402896)

Gao W, et al. Post-challenge hyperglycaemia rather than fasting hyperglycaemia is an independent risk factor of cardiovascular disease events. Clin Lab. 2004;50(9-10):609-15.
Yamagishi SI, et al. Role of postprandial hyperglycaemia in cardiovascular disease in diabetes. Int J Clin Pract. 2007 Jan;61(1):83-7.
Yoo HJ, et al. Use of a real time continuous glucose monitoring system as a motivational device for poorly controlled type 2 diabetes. Diabetes Res Clin Pract. 2008 Oct;82(1):73-9

# Other Considerations

- C-peptide
  - Assess the degree of remaining pancreatic function
  - Can be done during OGTT (15 minutes) to assess 1st phase insulin secretion
- BMI, waist circumference (WC), muscle strength
  - WC > 88cm alone is nearly as good at predicting insulin resistance in women as Met-S criteria
  - Body mass index, muscle strength, and cardiorespiratory fitness were better predictors in men
- The TyG index
  - Product of fasting triglycerides and glucose levels
  - Sensitivity 84.0% & Specificity 45.0% for detecting individuals with insulin resistance

Brandenburg D. History and diagnostic significance of C-peptide. Exp Diabetes Res. 2008;2008:576862.
Nilsson G, et al. Waist circumference alone predicts insulin resistance as good as the metabolic syndrome in elderly women. Eur J Intern Med. 2008 Nov;19(7):520-6.
Chen CN, Chuang LM, Wu YT. Clinical measures of physical fitness predict insulin resistance in people at risk for diabetes. Phys Ther. 2008 Nov;88(11):1355-64.
Simental-Mendía LE, Rodríguez-Morán M, et al. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. Metab Syndr Relat Disord. 2008 Winter;6(4):299-304.

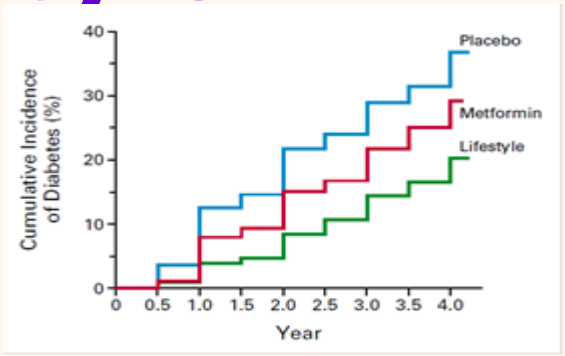
# Treatment Goals?

- Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial
- Intensive medical therapy (aimed at achieving HbA1c less than 6.0) vs. standard therapy (goal of 7.0-7.9) lowered 5 year rate of MI
- However, intensive arm of trial was halted, because increased 5 year overall mortality
- Drugs are not a substitute for healthy diet, needed nutrients and exercise!

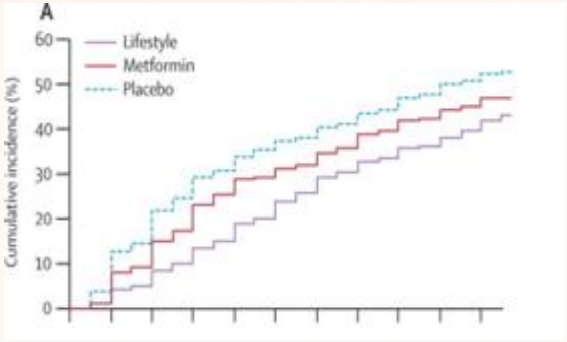
ACCORD Study Group, et al. Long-term effects of intensive glucose lowering on cardiovascular outcomes. N Engl J Med. 2011 Mar 3;364(9):818-28.

# Treatment - Lifestyle

- Combination of diet and physical activity has greatest benefit
- 3,000 non-diabetic with elevated fasting and post-load plasma glucose concentrations, lifestyle interventions reduced the incidence of T2D by 58%, and Metformin only by 31%, versus placebo
- At 10 year follow-up, diabetes incidence was reduced by 34% (24-42) in the lifestyle group and 18% (7-28) in the Metformin group compared with placebo (note, this is after unblinding, and offering lifestyle intervention to all participants)
- Lifestyle delayed diagnosis nearly 4x Metformin




Knowler 2002




Lancet 2009

Knowler WC, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002 Feb 7;346(6):393-403.
Diabetes Prevention Program Research Group, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet. 2009 Nov 14;374(9702):1677-86.
Herman WH, et al. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. Ann Intern Med. 2005 Mar 1;142(5):323-32.

# Lifestyle Benefit

- Lifestyle vs. Metformin - Diabetes Prevention Program
  - Lifestyle reduced the incidence of the metabolic syndrome 41% vs only 17% for Metformin
  - Delayed the development of T2D by 11 and 3 years, respectively
  - Cost for each program per quality-adjusted life year (QALY) was approximately $1100 for the lifestyle intervention and $31,300 for the Metformin intervention
- Lifestyle intervention for 6 years had benefit up to 14 years after intervention
- Metformin loses efficacy in elderly, lifestyle does not

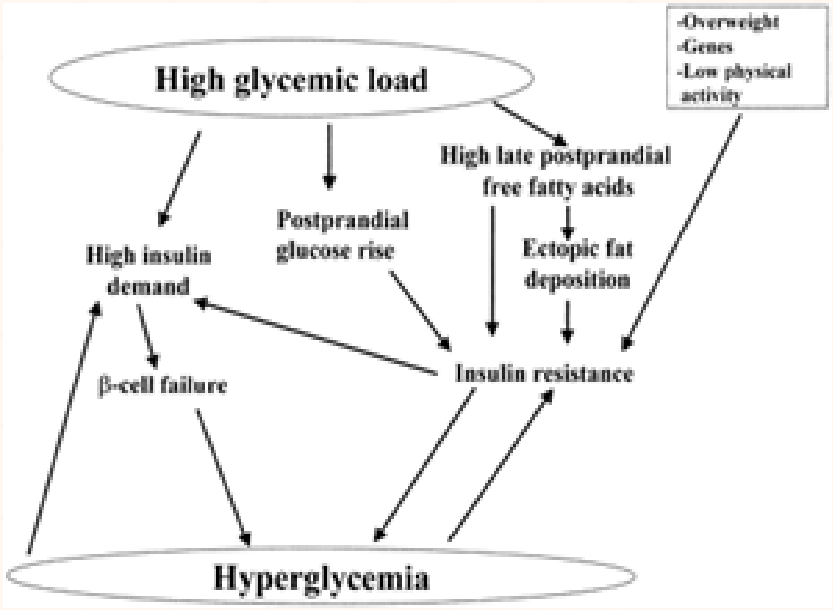
Orchard TJ, et al. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. Ann Intern Med. 2005 Apr 19;142(8):611-9.
Herman WH, et al. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. Ann Intern Med. 2005 Mar 1;142(5):323-32.
Li G, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. Lancet. 2008 May 24;371(9626):1783-9.
Diabetes Prevention Program Research Group, et al. The influence of age on the effects of lifestyle modification and metformin in prevention of diabetes. J Gerontol A Biol Sci Med Sci. 2006 Oct;61(10):1075-81.

# Dietary Approach

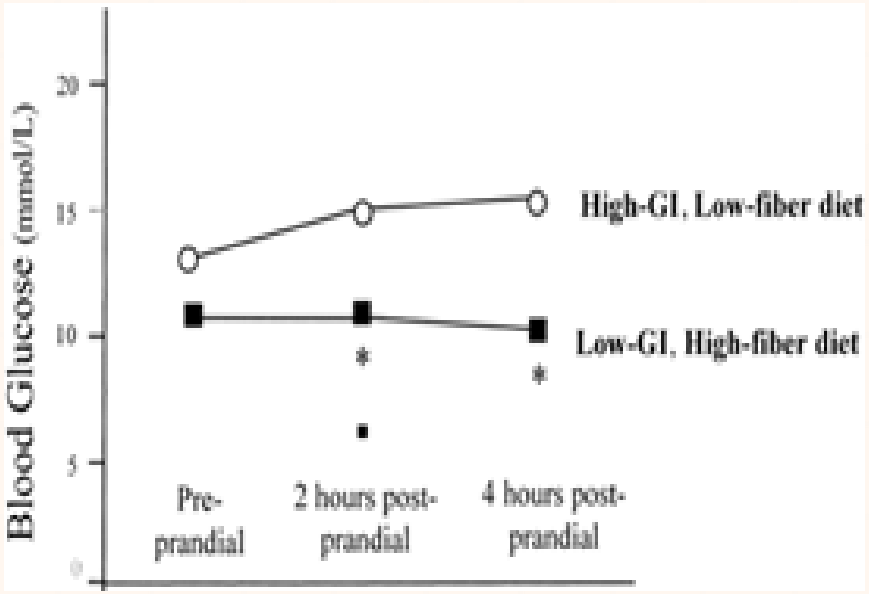
- Mediterranean diet
  - Improves glycemic control in normoglycemic populations, reduces (central) obesity risk
  - Prospective study of 14,000, highest adherence associated with a RR of 0.17 for diabetes
- Low glycemic
  - Review of 37 prospective cohort studies, RR of T2D was 1.40 for those consuming a high vs. low GI
  - Reduces postprandial hyperglycemia, and NF-KappaB activation
- High fiber
  - Multiple studies demonstrate lower risk for T2D with higher intake
  - Some fiber (psyllium, other fiber sources) shown to reduce glucose spike at next meal

Panagiotakos DB, et al. The association between adherence to the Mediterranean diet and fasting indices of glucose homoeostasis: the ATTICA Study. J Am Coll Nutr. 2007 Feb;26(1):32-8.
Martínez-González MA, et al. Adherence to Mediterranean diet and risk of developing diabetes: prospective cohort study. BMJ. 2008 Jun 14;336(7657):1348-51.
Barclay AW, et al. Glycemic index, glycemic load, and chronic disease risk--a meta-analysis of observational studies. Am J Clin Nutr. 2008 Mar;87(3):627-37.

# Fiber Reduces Glycemic Load




Riccardi 2008

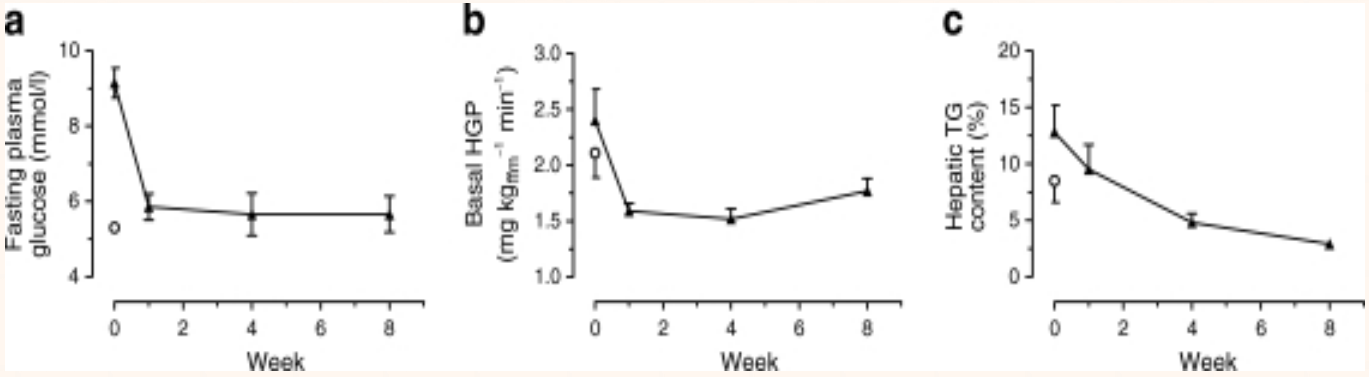



Riccardi 2008

Riccardi G, et al. Role of glycemic index and glycemic load in the healthy state, in prediabetes, and in diabetes. Am J Clin Nutr. 2008 Jan;87(1):269S-274S

# Low Calorie?

- Small trial – 11 diabetics & controls
  - Liquid diet formula (46.4% carbohydrate, 32.5% protein and 20.1% fat; vitamins, minerals and trace elements; 510 kcal/day
  - Supplemented with three portions of non-starchy vegetables
  - Total energy intake was about 600 kcal/day.
- *Normalization of both beta cell function and hepatic insulin sensitivity*
- At very least, shows dysfunction is reversible




Lim 2011

Lim EL, et al. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Diabetologia. 2011 Oct;54(10):2506-14.

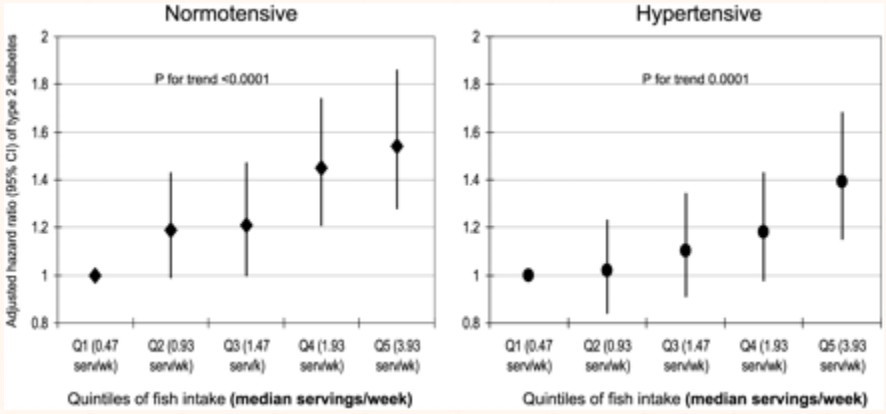
# Other Dietary Factors

- Monounsaturated fatty acids (MUFAs) restore beta-cell function & insulin sensitivity
  - Higher intake linked to lower neuropathy in diabetics
  - Saturated fats and trans fats are known to increase postprandial insulinemia, as well as endothelial dysfunction
- Eating meals regularly associated with lower risk for both Met-S and insulin resistance in study of 3600
  - Small study: largest carbohydrate intake at lunch associated with the most favorable postprandial profile – spacing out carbs did not have benefit

Tao M, et al. Relationship of polyunsaturated fatty acid intake to peripheral neuropathy among adults with diabetes in the National Health and Nutrition Examination Survey (NHANES) 1999 2004. Diabetes Care. 2008 Jan;31(1):93-5.
Sierra-Johnson J, et al. Eating meals irregularly: a novel environmental risk factor for the metabolic syndrome. Obesity (Silver Spring). 2008 Jun;16(6):1302-7.
Pearce KL, et al. Effect of carbohydrate distribution on postprandial glucose peaks with the use of continuous glucose monitoring in type 2 diabetes. Am J Clin Nutr. 2008 Mar;87(3):638-44

# Essential Fatty Acids

- Omega-3 fatty acids – mixed findings
  - Appear to have neutral effect on insulin sensitivity, but reduce cardiovascular mortality/morbidity among diabetics
  - Surprisingly, however, large prospective studies (Women's Health Study, Nurse's Health study 1 & 2) show increased risk for diabetes when consumed above a threshold, particularly in women
- Plant based omega-3 oils not associated with increased risk
- Omega-3's reduce triglycerides, improve composition of LDL-C (increase large buoyant particles)




Djoussé L, et al. Dietary omega-3 fatty acids and fish consumption and risk of type 2 diabetes. Am J Clin Nutr. 2011 Jan;93(1):143-50.

Ouguerram K, et al. Effect of n-3 fatty acids on metabolism of apoB100-containing lipoprotein in type 2 diabetic subjects. Br J Nutr. 2006 Jul;96(1):100-6.

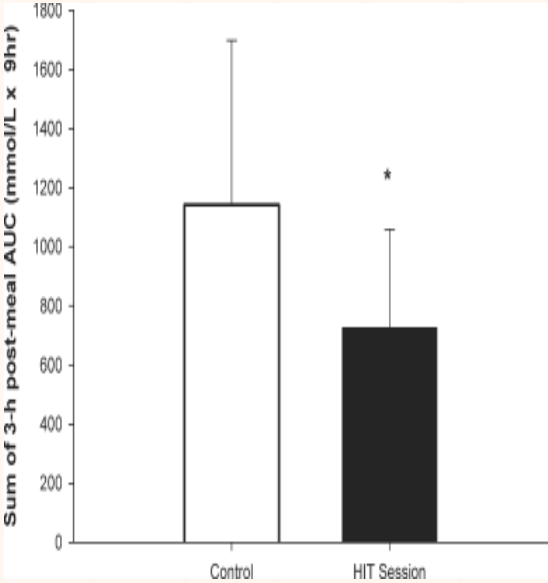
# Physical Activity

- Muscle strengthening activity has been shown to be independently associated with higher insulin sensitivity
- Combination of aerobic and resistance most effective for lowering HbA1c
- Combined aerobic & resistant training shown to partly reverse mitochondrial deficits among long-standing diabetics
- Exercise while fasting improves glucose tolerance
- Muscle mass stabilizes blood sugar!

Van Proeyen K et al. Training in the fasted state improves glucose tolerance during fat-rich diet. J Physiol. 2010 Nov 1;588(Pt 21):4289-302.
Sigal RJ, et al. Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes: a randomized trial. Ann Intern Med. 2007 Sep 18;147(6):357-69.
van Tienen FH, et al. Physical Activity Is the Key Determinant of Skeletal Muscle Mitochondrial Function in Type 2 Diabetes. J Clin Endocrinol Metab. 2012 Jul 16. [Epub ahead of print]

# High-Intensity Interval Exercise

- Brief repeated bursts of relatively intense exercise separated by periods of recovery
- Time-efficient strategy
- Using continuous glucose monitoring, shown to reduce postprandial hyperglycaemia in patients with T2D after single session
- Also shown to improve muscle mitochondrial capacity in patients with T2D




Gillen 2012

Gillen JB, Acute high-intensity interval exercise reduces the postprandial glucose response and prevalence of hyperglycaemia in patients with type 2 diabetes. Diabetes Obes Metab. 2012 Jun;14(6):575-7. doi: 10.1111/j.1463-1326.2012.01564.x.
Little JP, et al. Low-volume high-intensity interval training reduces hyperglycemia and increases muscle mitochondrial capacity in patients with type 2 diabetes. J Appl Physiol. 2011 Dec;111(6):1554-60.

# Key Nutrients

- Chromium
  - Benefits include improved insulin sensitivity, HbA1c reduction, central obesity, and glucose control
- Vitamin D
  - Insufficiency increases inflammation, risk for diabetes and insulin resistance. Supplementation improves insulin sensitivity
- Fibre
  - Stabilizes blood sugar, delays and decreases postprandial hyperglycemia
- Magnesium
  - Deficiency independently associated with the development of (IGT) and T2D
  - Review of 9 randomized trials with T2D patients, magnesium was shown to have raised HDL and lowered fasting plasma glucose

Nagpal J, et al. A double-blind, randomized, placebo-controlled trial of the short-term effect of vitamin D3 supplementation on insulin sensitivity in apparently healthy, middle-aged, centrally obese men. Diabet Med. 2009 Jan;26(1):19-27.
Martin J, et al. Chromium picolinate supplementation attenuates body weight gain and increases insulin sensitivity in subjects with type 2 diabetes. Diabetes Care. 2006 Aug;29(8):1826-32.
Song Y, et al. Effects of oral magnesium supplementation on glycaemic control in Type 2 diabetes: a meta-analysis of randomized double-blind controlled trials. Diabet Med. 2006 Oct;23(10):1050-6.
Guerrero-Romero F, et al. Hypomagnesaemia and risk for metabolic glucose disorders: a 10-year follow-up study. Eur J Clin Invest. 2008 Jun;38(6):389-96.

# Key Nutrients

- Antioxidants
  - CoQ10
    - Improves blood pressure, oxidative status, HbA1c, and glycemic control in diabetic patients
    - Mitochondrial function impaired in individuals with insulin resistance and T2D, and also in their offspring
    - Levels are decreased among T2D, and negative correlation between plasma CoQ10 and HbA1c
  - Alpha lipoic acid
    - Improves glycemic control and insulin resistance, prevents complications of hyperglycemia
- Acetyl l-carnitine
  - Improves neuropathy symptoms as well as neuronal degeneration

Hodgson JM, et al. Coenzyme Q10 improves blood pressure and glycaemic control: a controlled trial in subjects with type 2 diabetes. Eur J Clin Nutr. 2002 Nov;56(11):1137-42.
Petersen KF, et al. Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. N Engl J Med. 2004 Feb 12;350(7):664-71.
Tang J, et al. Alpha-lipoic acid may improve symptomatic diabetic polyneuropathy. Neurologist. 2007 May;13(3):164-7.
El-ghoroury EA, et al. Malondialdehyde and coenzyme Q10 in platelets and serum in type 2 diabetes mellitus: correlation with glycemic control. Blood Coagul Fibrinolysis. 2009 Jun;20(4):248-51.

# Herbal Medicines

- *Panax ginseng*
  - Reduced fasting plasma glucose, HbA1c, and postprandial hyperglycemia in trials with non-diabetic and T2D patients
  - But overall small clinical effect
  - Recent study found no benefit, points to poor bioavailability
- Fenugreek
  - Improvements in fasting plasma glucose and oral glucose tolerance in T1D patients. Similar in T2D
- Green tea, bitter melon, and *Gymnema* suggestive of benefit, but less well established

Vuksan V, et al. Korean red ginseng (Panax ginseng) improves glucose and insulin regulation in well-controlled, type 2 diabetes: results of a randomized, double-blind, placebo-controlled study of efficacy and safety. Nutr Metab Cardiovasc Dis. 2008 Jan;18(1):46-56.
Reeds DN, et al. Ginseng and Ginsenoside Re Do Not Improve {beta}-Cell Function or Insulin Sensitivity in Overweight and Obese Subjects with Impaired Glucose Tolerance or Diabetes. Diabetes Care. 2011 Mar 16.
Gupta A. Effect of Trigonella foenum-graecum (fenugreek) seeds on glycaemic control and insulin resistance in type 2 diabetes mellitus: a double blind placebo controlled study. J Assoc Physicians India. 2001 Nov;49:1057-61.

# Considerations for POP Toxicity

- Treatment Strategy
  - Decrease Exposure!!
    - Organic, mostly plant-based diet
    - Natural HABAs
  - Increase glutathione production
  - Supportive therapies
    - Antioxidant support
    - Detoxification support
    - Methylation support
  - Specific therapies
    - Systemic detoxification
    - Sauna
    - Fasting

# Glutathione Conjugation Main Route of POP Detox

- Many POPs are eliminated by phase I biotransformation, followed by phase II conjugation to glutathione (GSH)
- GSH plays a crucial role against endogenously generated reactive oxygen/nitrogen species
- GSH levels decline as conjugation reactions exceed cells ability to regenerate GSH
- PCBs and organochlorine pesticides increase oxidative damage and deplete glutathione levels


Awasthi YC, et al. Physiological and pharmacological significance of glutathione-conjugate transport. J Toxicol Environ Health B Crit Rev. 2009 Aug;12(7):540-51.

Ludewig G et al. Mechanisms of toxicity of PCB metabolites: generation of reactive oxygen species and glutathione depletion. Cent Eur J Public Health. 2000 Jul;8 Suppl:15-7.

Ahmed T, Endosulfan-induced apoptosis and glutathione depletion in human peripheral blood mononuclear cells: Attenuation by N-acetylcysteine. J Biochem Mol Toxicol. 2008 Sep;22(5):299-304.

# Clinical Outcomes of GSH-based Therapy

- Diabetic hypertensive men (randomized placebo-controlled)
  - NAC (600mg bid) given with L-arginine (1200mg qd)
  - Lowered blood pressure, and improved many markers of endothelial function and inflammation, including C-reactive protein, fibrinogen, and LDL-cholesterol
- Poorly controlled type 2 diabetes
  - Markers of glutathione synthesis and plasma oxidative stress were both improved
  - 0.81 mmol/kg/day of cysteine (given as NAC) and 1.33 mmol/kg/day of glycine

Martina V et al. Long-term N-acetylcysteine and L-arginine administration reduces endothelial activation and systolic blood pressure in hypertensive patients with type 2 diabetes. Diabetes Care. 2008 May;31(5):940-4.
Sekhar et al. Glutathione synthesis is diminished in patients with uncontrolled diabetes and restored by dietary supplementation with cysteine and glycine. Diabetes Care. 2011 Jan;34(1):162-7.

# Curcumin – Multiple Targets

- Potent anti-inflammatory, with multiple molecular targets, with specific benefit for diabetes, Met-S, and insulin resistance
- Curcumin interacts with proteins in adipocytes, pancreatic cells, hepatic stellate cells, macrophages, and muscle cells
- Curcumin reverses insulin resistance, hyperglycemia, hyperlipidemia, and other inflammatory symptoms associated with obesity and metabolic diseases
- Curcumin prevented effect of AGEs on hepatic stellate cells, via activating PPARγ and attenuating oxidative stress

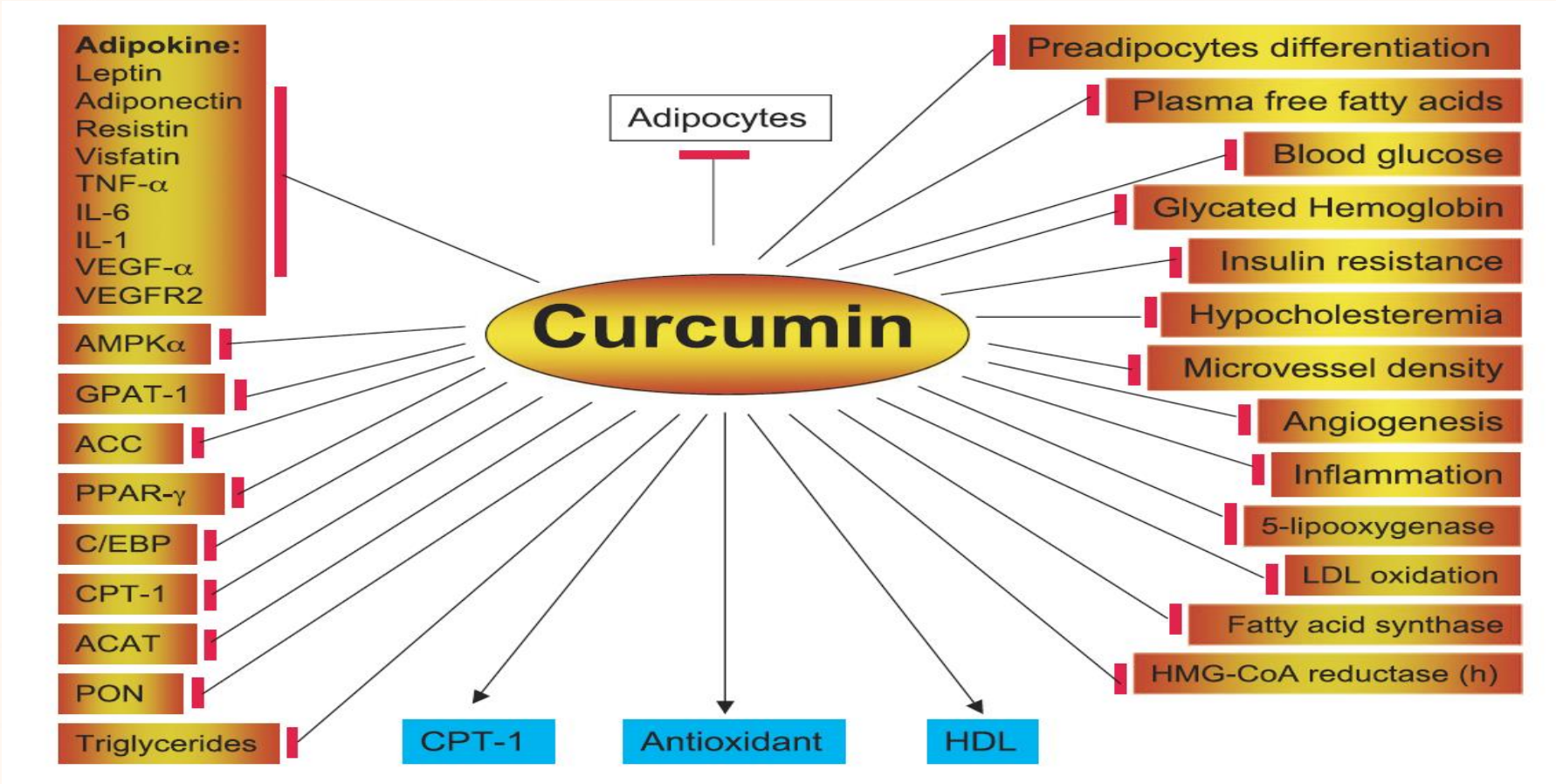
Shehzad A, et al. New mechanisms and the anti-inflammatory role of curcumin in obesity and obesity-related metabolic diseases. Eur J Nutr. 2011 Apr;50(3):151-61.
Lubbad A, Oriowo MA, Khan I. Curcumin attenuates inflammation through inhibition of TLR-4 receptor in experimental colitis. Mol Cell Biochem. 2008 Nov 11.
Lin J, et al. Curcumin inhibits advanced glycation end-products (AGEs)-induced gene expression of receptor for AGEs (RAGE) in hepatic stellate cells in vitro by elevating PPARγ activity and attenuating oxidative stress. Br J Pharmacol. 2012 Feb 21. doi: 10.1111/j.1476-5381.2012.01910.x.

# Curcumin Targets

- Inhibits an enzyme (p300, a histone acetyltransferase) known to be involved in complications of diabetes, as well as heart failure and cardiac hypertrophy
- Curcumin decreases hyperglycemia-induced cytokine production in monocytes via epigenetic changes involving NF-κB – may reduce vascular inflammation & diabetic complications
- Curcumin had synergistic effect with insulin on muscle cells, increasing insulin sensitivity (mediated by basal glucose translocation of GLUT4)

Chiu J, et al. Curcumin prevents diabetes-associated abnormalities in the kidneys by inhibiting p300 and nuclear factor-kappaB. Nutrition. 2009 Sep;25(9):964-72.
Yun et al. Epigenetic regulation of high glucose-induced proinflammatory cytokine production in monocytes by curcumin. J Nutr Biochem. 2011 May ; 22(5): 450–458. doi:10.1016/j.jnutbio.2010.03.014
Kang C et al. Synergistic effect of curcumin and insulin on muscle cell glucose metabolism. Food Chem Toxicol. 2010 Aug-Sep;48(8-9):2366-73.

# Multiple Targets



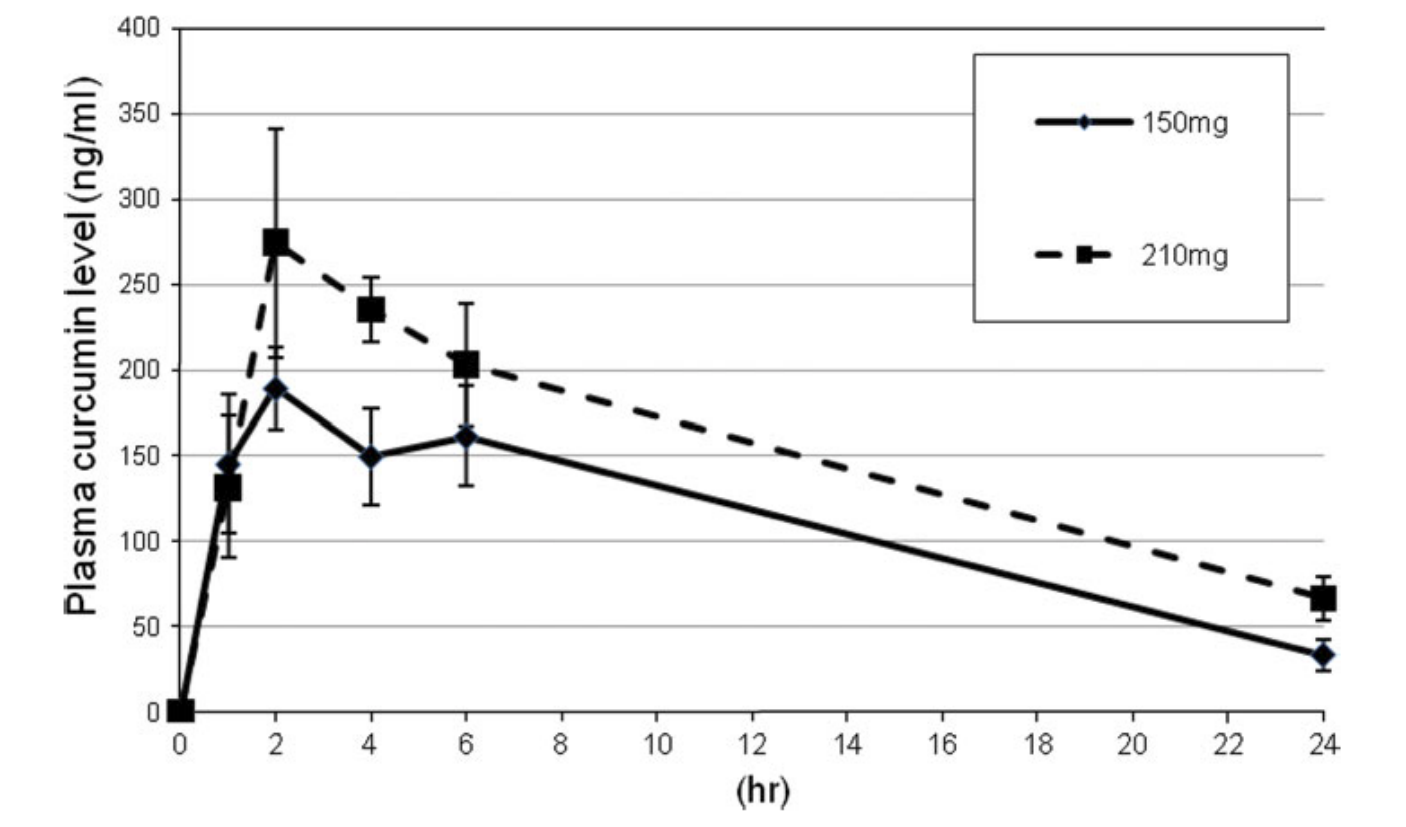

Aggarwal BB. Targeting inflammation-induced obesity and metabolic diseases by curcumin and other nutraceuticals. Annu Rev Nutr. 2010 Aug 21;30:173-99.

# Curcumin Human Trials

- Double-blind supplementation with turmeric among diabetics with nephropathy
  - Attenuated proteinuria, and other risk factors (TGF-β , IL-8)
- 4-week trial of 25 diabetics with lecithinized formulation of curcumin
  - Improved microcirculatory signs in all patients, with no benefit observed in control group

Khajehdehi P, et al. Oral supplementation of turmeric attenuates proteinuria, transforming growth factor-β and interleukin-8 levels in patients with overt type 2 diabetic nephropathy: a randomized, double-blind and placebo-controlled study. Scand J Urol Nephrol. 2011 Nov;45(5):365-70.
Appendino G, et al. Potential role of curcumin phytosome (Meriva) in controlling the evolution of diabetic microangiopathy. A pilot study. Panminerva Med. 2011 Sep;53(3 Suppl 1):43-9.

# Dose–Dependent Bioavailability

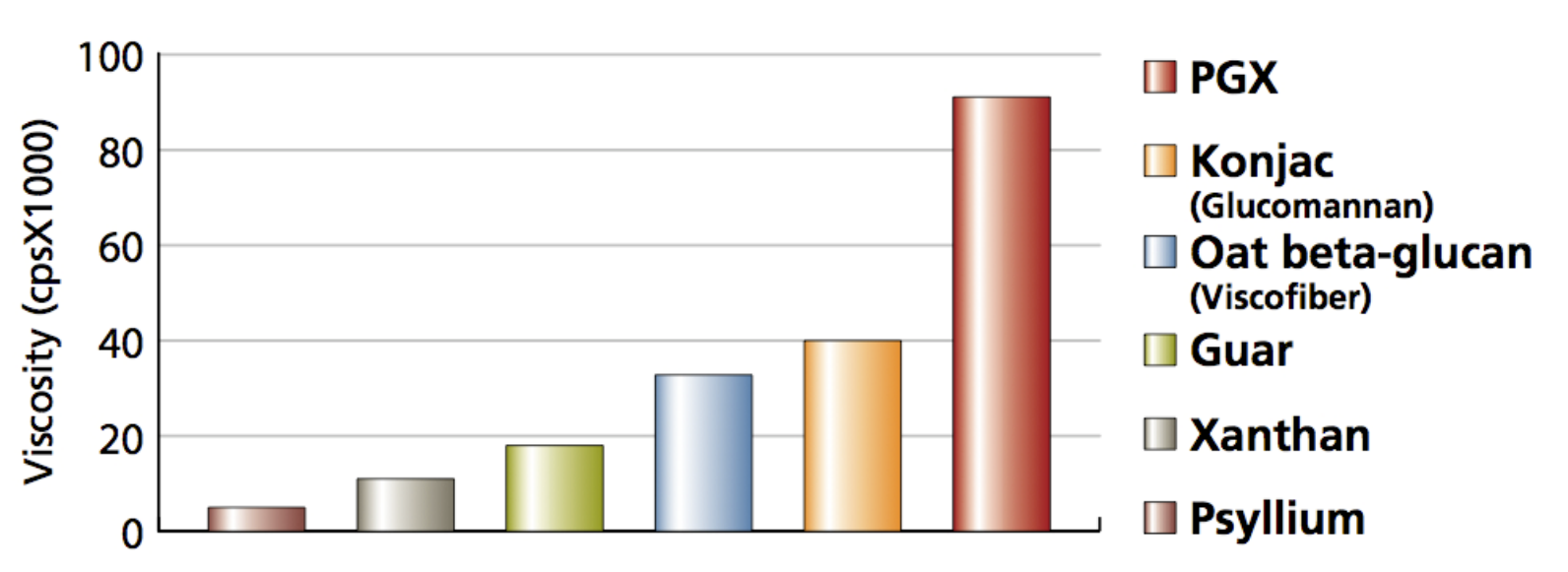



Kanai M, et al. Dose-escalation and pharmacokinetic study of nanoparticle curcumin, a potential anticancer agent with improved bioavailability, in healthy human volunteers. Cancer Chemother Pharmacol. 2012 Jan;69(1):65-70.

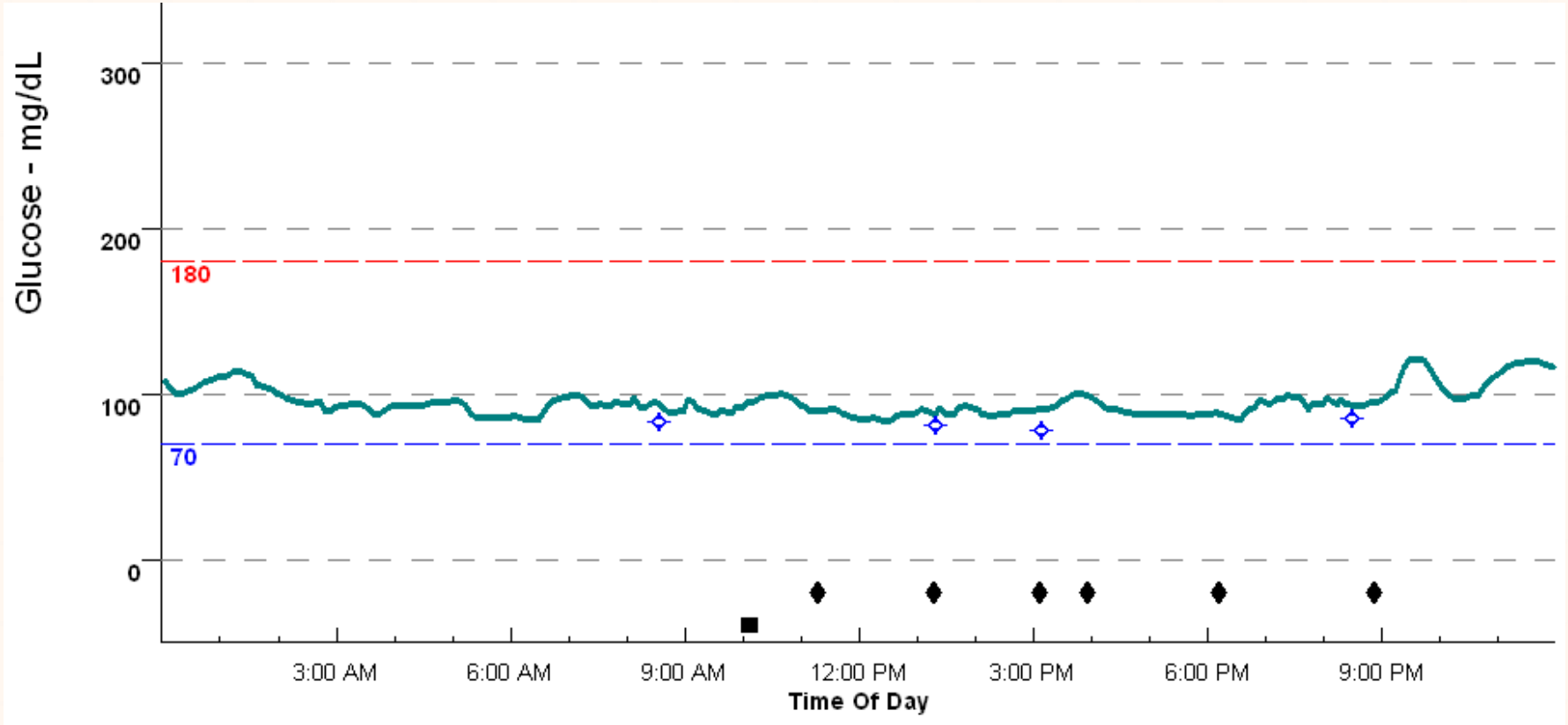
# PGX® (PolyGlycopleX)

- Proprietary soluble fiber with exceptional viscosity – patent pending.
  - *Konjac glucomannan*
  - Xanthan gum
  - Sodium alginate
- PGX is NOT a blend
  - IUPAC (International Union of Pure and Applied Chemistry) name : (α-D-glucurono-α-D-manno-β-D-manno-β-D-gluco), (α-L-gulurono-β-D mannurono), β-D-gluco-β-D-mannan
- PGX possesses unique physical qualities and physiological benefits
- Binds more than 600 times its weight in water.
- Produces clinical results at practical dosages.

# PGX Compared to Other Plant Fibers



# Importance of Fiber
## (Same Patient on PGX)



# Blood Glucose Instability Leads to Weight Gain and Impaired Glucose Tolerance

International Journal of Obesity (2009) 33, 46–53

0307-0565/09 $32.00
www.nature.com/ijo

REVIEW

## The glucostatic theory of appetite control and the risk of obesity and diabetes

J-P Chaput and A Tremblay

*Division of Kinesiology, Faculty of Medicine, Department of Social and Preventive Medicine, Laval University, Quebec City, Quebec, Canada*

More than 50 years ago, Jean Mayer proposed that changes in blood glucose concentrations or arteriovenous glucose differences are detected by glucoreceptors that affect energy intake. According to this theory, an increase in blood glucose concentrations results in increased feelings of satiety whereas a drop in blood glucose concentrations has the opposite effect. The pioneering work of Mayer has recently received support from our group as low glycemia has been shown to be linked with body weight gain prospectively and has been considered as a strong predictor of the amount of weight regained after weight loss. This state of mild hypoglycemia also predicts the increase in depressive symptoms with weight loss and a greater propensity to glucose intolerance and type 2 diabetes, particularly for individuals having short sleep durations. Furthermore, knowledge-based work has been shown to induce a significant increase in spontaneous energy intake being related to changes in glycemic control. In accordance with the glucostatic theory, this oriented review suggests that factors favoring a trend toward hypoglycemia and/or glucose instability might induce excess energy intake, overweight and impaired glucose tolerance. Data also raise the possibility that fat gain might be protective against mild hypoglycemia by providing compensation to the stimuli promoted by a modern environment.

# Low-glycemic Foods or Meals Have Higher Satietogenic Effect Than High-glycemic Foods or Meals

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Appetite 49 (2007) 535–553
Appetite
www.elsevier.com/locate/appet

Research Review

## Glycaemic response to foods: Impact on satiety and long-term weight regulation

Francis R.J. Bornet[a,*], Anne-Elodie Jardy-Gennetier[a], Noémie Jacquet[a], Julian Stowell[b]

[a]*NUTRI-HEALTH S.A., Immeuble AMPERE, 8 rue Eugène et Armand Peugeot, 92566 Rueil-Malmaison Cedex, France*
[b]*DANISCO SWEETENERS LTD, 41/51 Brighton Road, Redhill, Surrey RH1 6YS, UK*

Received 17 November 2006; received in revised form 20 April 2007; accepted 24 April 2007

**Abstract**

Should future nutritional recommendations for the general population take into account the notion of glycaemic index (GI)? This question is all the more legitimate as the glycaemic response to foods seems to be a factor that affects satiety and could therefore affect food intake. The aim of this review was to evaluate whether altering the glycaemic response *per se* can modulate satiety and to assess the short-term and long-term consequences. A systematic review of human intervention studies was performed. Confounding factors that

# PGX is Safe (5% Rat Diet → No Adverse Effects)

**Nutrition Journal**

BioMed Central

Research

Open Access

## The safety of PolyGlycopleX® (PGX®) as shown in a 90-day rodent feeding study

Ray A Matulka*†[1], Michael R Lyon†[2,3], Simon Wood†[2], Palma Ann Marone†[4], Daniel J Merkel†[4] and George A Burdock†[1]

Address: [1]Burdock Group, 801 North Orange Avenue, Suite 710, Orlando, FL 32801 USA, [2]Canadian Centre for Functional Medicine, 1552 United Boulevard, Coquitlam, BC, V3K 6Y2, Canada , [3]University of British Columbia, Food, Nutrition and Health Program, 2357 Main Mall, Vancouver, B.C., V6T 1Z4, Canada and [4]Eurofins|Product Safety Laboratories, 2394 Highway 130, Dayton, NJ 08810 USA

Email: Ray A Matulka* - rmatulka@burdockgroup.com; Michael R Lyon - doctorlyon@shaw.ca; Simon Wood - simonwood@shaw.ca; Palma Ann Marone - PamMarone@productsafetylabs.com; Daniel J Merkel - DanMerkel@productsafetylabs.com; George A Burdock - gburdock@burdockgroup.com

* Corresponding author †Equal contributors

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Received: 3 September 2008
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# PGX, Non-Mutagenic

International
Journal of Toxicology
Volume 28 Number 4
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http://online.sagepub.com

## Genotoxicity Studies of PolyGlycopleX (PGX)

### A Novel Dietary Fiber

Palma Ann Marone, Michael Lyon, Roland Gahler,
Claudia Donath, Hana Hofman-Hüther, and Simon Wood

PolyGlycopleX (PGX), a novel dietary fiber, produces no mutagenic effects in bacterial tester strains *Salmonella typhimurium* TA 98, TA 100, TA 1535, and TA 1537 and *Escherichia coli* WP2 uvrA at concentrations of 0.316, 1.00, 3.16, 10.0, 31.6, and 100 µg/plate. No biologically relevant increases in revertant colonies of any of the 5 strains are observed at any concentration; however, a reduction at 100 µg/plate in TA 1537 is noted. PGX, analyzed for polychromatic erythrocyte micronuclei induction in mice following a single 1×, 0.5×, and 0.2× maximum tolerable dose intraperitoneal treatment, produces no biologically relevant increase in any dose group. Males at 1× maximum tolerable dose show a reduction of micronuclei-containing cells. High-dose animals show signs of systemic toxicity, including a reduction of spontaneous activity, rough fur, palpebral closure, prone position, and constricted abdomen. These genotoxicity studies show PGX to be nonmutagenic in both the Ames bacterial reverse mutation assay and the mammalian erythrocyte micronucleus test.

**Keywords:** Ames test; dietary fiber; genotoxicity; mammalian erythrocyte micronucleus; PGX

# PGX, Well Tolerated Clinically

**Nutrition Journal**

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Research

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## Supplementation of the diet with the functional fiber PolyGlycoplex® is well tolerated by healthy subjects in a clinical trial

Ioana G Carabin*[1], Michael R Lyon[2,3], Simon Wood[2], Xavier Pelletier[4], Yves Donazzolo[4] and George A Burdock[1]

Address: [1]Burdock Group, Orlando, Florida, USA, [2]Canadian Centre for Functional Medicine, Coquitlam, British Columbia, Canada, [3]Food, Nutrition and Health Program, University of British Columbia, Coquitlam, British Columbia, Canada and [4]OPTIMED Clinical Research, Gieres, France

Email: Ioana G Carabin* - icarabin@burdockgroup.com; Michael R Lyon - doctorlyon@shaw.ca; Simon Wood - simonwood@shaw.ca; Xavier Pelletier - xavier.pelletier@optimed.fr; Yves Donazzolo - yves.donazzolo@optimed.fr; George A Burdock - gburdock@burdockgroup.com

* Corresponding author

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This article is available from: http://www.nutritionj.com/content/8/1/9

# PGX Increases Satiety Hormone (PYY) and Decreases Insulin

European Journal of Clinical Nutrition (2010), 1–6

0954-3007/10 $32.00
www.nature.com/ejcn

ORIGINAL ARTICLE

## Increased plasma PYY levels following supplementation with the functional fiber PolyGlycopleX in healthy adults

RA Reimer[1], X Pelletier[2], IG Carabin[3], M Lyon[4,5], R Gahler[6], JA Parnell[7] and S Wood[4]

[1]*Faculty of Kinesiology and Department of Biochemistry and Molecular Biology, University of Calgary, Calgary, Alberta, Canada;* [2]*OPTIMED Clinical Research, Gieres, France;* [3]*Burdock Group, Orlando, FL, USA;* [4]*Canadian Centre for Functional Medicine, Coquitlam, British Columbia, Canada;* [5]*University of British Columbia, Food, Nutrition and Health Program, Vancouver, British Columbia, Canada;* [6]*Factors Group of Nutritional Studies Inc. R & D, Burnaby, British Columbia, Canada and* [7]*Department of Physical Education and Recreation Studies, Mount Royal University, Calgary, Alberta, Canada*

**Background/Objectives:** A variety of dietary fibers have been shown to alter satiety hormone gene expression and secretion. The objective of this study was to examine plasma satiety hormone concentrations in healthy subjects consuming either PolyGlycopleX (PGX) or control (skim milk powder) for 21 days.
**Subjects/Methods:** A randomized, double-blind, placebo-controlled clinical study was conducted in 54 healthy male and female adults. Participants consumed 5 g per day of PGX or control for 1 week followed by 2 additional weeks of 10 g per day of assigned product ($n = 27$ per group). Primary outcomes measured at three visits (V1, V2 and V3) were plasma active glucagon-like peptide-1 (GLP-1) total ghrelin, peptide YY (PYY) and insulin.
**Results:** There was a significant effect of visit for fasting PYY with control participants experiencing decreased PYY levels over time while PGX prevented this decline. When stratified by body mass index (BMI), PGX increased fasting PYY levels from week 1 to week 3 compared with control in participants with BMI $< 23$ kg/m$^2$. There was a significant effect of visit for fasting ghrelin with levels decreasing in both PGX and control groups over time. No differences were detected in fasting GLP-1 levels. Although there was a 14% reduction in fasting insulin between V1 and V3 with PGX this was not significantly different from control.
**Conclusions:** PGX is a highly viscous, functional fiber that modifies satiety hormone secretion in healthy adults. Its' potential to act similarly in overweight adults warrants investigation.
*European Journal of Clinical Nutrition* advance online publication, 28 July 2010; doi:10.1038/ejcn.2010.141

**Keywords:** functional fiber; viscosity; satiety hormones; peptide YY; GLP-1

# PGX Delays and Decreases Postprandial Glycaemia

Open

European Journal of Clinical Nutrition (2010), 1–6

0954-3007/10
www.nature.com/ejcn

ORIGINAL ARTICLE

## Effects of PGX, a novel functional fibre, on acute and delayed postprandial glycaemia

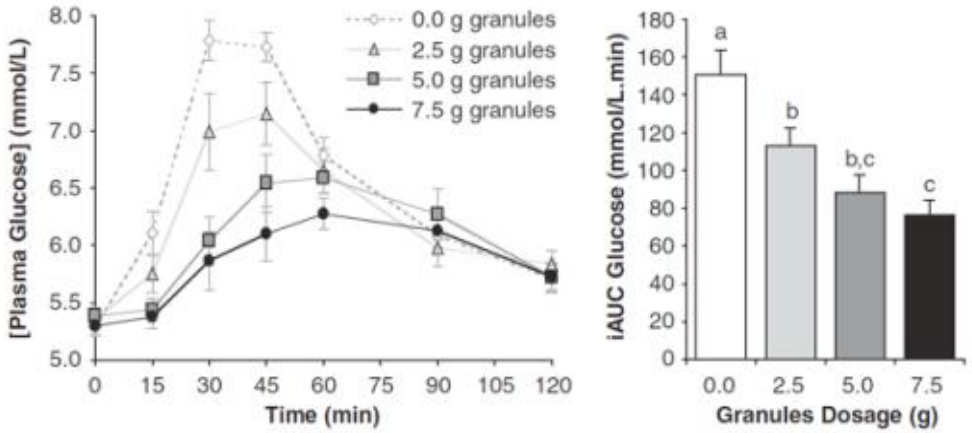



**Figure 1** Acute dose–response effects. Incremental postprandial blood glucose responses and corresponding incremental area under the curve (iAUC) of 10 healthy subjects after four meals containing 50 g available carbohydrate as white bread supplemented with 0, 2.5, 5 or 7.5 g of PGX granules dissolved in 500 ml of water. Columns with different letters are significantly different ($P<0.01$). *P*-values are for analysis of variance with pairwise comparisons.

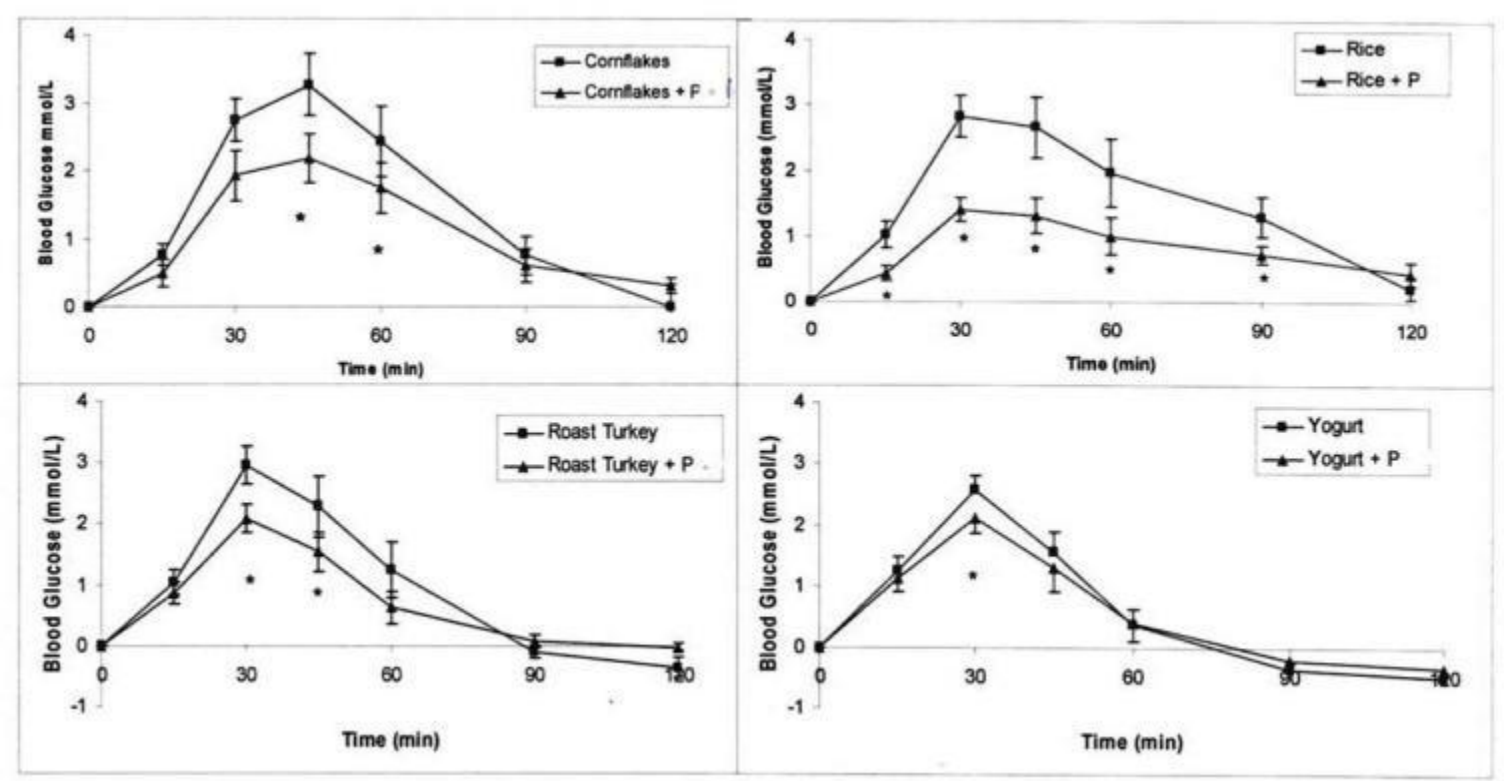
# PGX Decreases Glycemic Index of Foods

Jenkins et al. Nutrition Journal 2010, 9:58
http://www.nutritionj.com/content/9/1/58

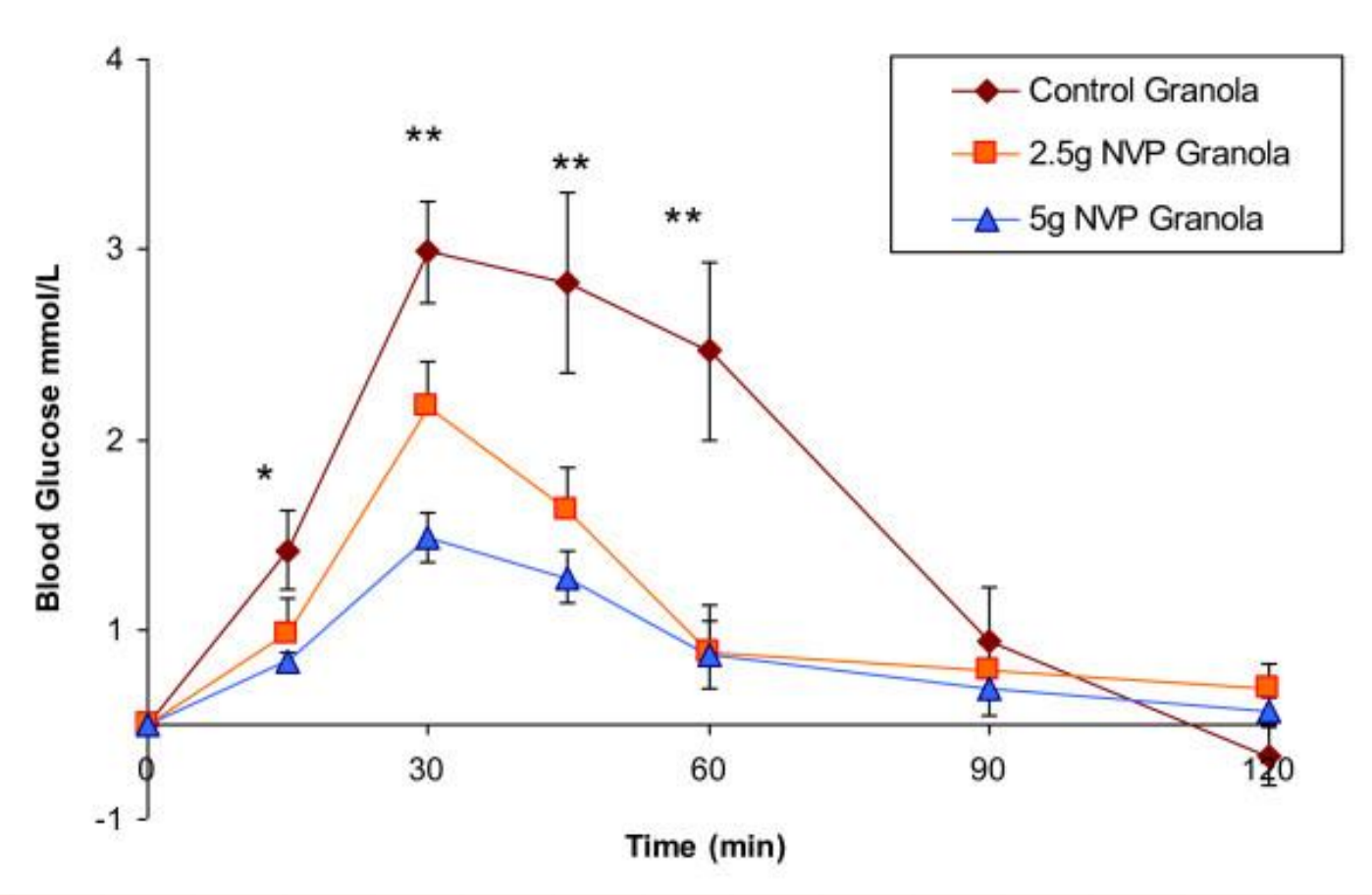
NUTRITION JOURNAL

RESEARCH Open Access

Effect of adding the novel fiber, PGX®, to commonly consumed foods on glycemic



# Incorporation of PGX into Granola



# Fiber Pre-Meal Decreases Food Intake

Nutrition, Metabolism & Cardiovascular Diseases (2009) 19, 498–503

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Nutrition, Metabolism & Cardiovascular Diseases

## Viscosity of fiber preloads affects food intake in adolescents

V. Vuksan [a,b,c,e,*], S. Panahi [a], M. Lyon [d], A.L. Rogovik [c], A.L. Jenkins [c], L.A. Leiter [a,b,c,e]

[a] Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
[b] Department of Medicine, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
[c] Clinical Nutrition and Risk Factor Modification Center, St. Michael's Hospital and Li Ka Shing Knowledge Institute, Toronto, Ontario, Canada
[d] Canadian Centre for Functional Medicine, Coquitlam and Food, Nutrition and Health Program, Faculty of Land and Food Systems, University of British Colombia, Vancouver, British Columbia, Canada
[e] Division of Endocrinology and Metabolism, St. Michael's Hospital, Toronto, Ontario, Canada

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KEYWORDS
Food intake;
Satiety;
Viscous dietary fiber;
Adolescents

Abstract *Background and aims:* Dietary fiber that develops viscosity in the gastrointestinal tract is capable of addressing various aspects of food intake control. The aim of this study was to assess subsequent food intake and appetite in relation to the level of viscosity following three liquid preloads each containing 5 g of either a high (novel viscous polysaccharide; NVP), medium (glucomannan; GLM), or low (cellulose; CE) viscosity fiber.
*Methods and results:* In this double-blind, randomized, controlled and crossover trial, 31 healthy weight adolescents (25 F:6 M; age 16.1 ± 0.6 years; BMI 22.2 ± 3.7 kg/m$^2$) consumed one of the three preloads 90 min prior to an *ad libitum* pizza meal. Preloads were identical

# PGX Facilitates Weight Loss

## The Effect of a Novel Viscous Polysaccharide along with Lifestyle Changes on Short-Term Weight Loss and Associated Risk Factors in Overweight and Obese Adults: An Observational Retrospective Clinical Program Analysis

Michael R. Lyon, MD, and Ronald G. Reichert, ND

Abstract

BACKGROUND: Viscous soluble dietary fiber has been demonstrated to reduce postprandial glycemia and may promote satiety. PolyGlycopleX® (PGX®) is a highly viscous polysaccharide manufactured by reacting glucomannan with other soluble polysaccharides using a proprietary process (EnviroSimplex®). The resulting polysaccharide (α-D-glucurono-α-D-manno-β-D-manno-β-D-glucan, α-L-gulurono-β-D-mannuronan, β-D-gluco-β-D-mannan, α-D-glucurono-α-D-manno-β-D-manno-β-D-gluco, α-L-gulurono-β-D-mannurono, β-D-gluco-β-D-mannan) is a novel entity with the highest viscosity and water-holding capacity of currently known fibers. MATERIALS & METHODS: A total of 29 sedentary overweight or obese adults (23 women; six men), ages 20-65 with a body mass index (BMI) range of 25 kg/m$^2$ to 36 kg/m$^2$ participated in a clinical weight-loss program. PGX (5 g) was consumed with 500 mL water, 5-10 minutes before each meal, 2-3 times daily for 14 weeks. RESULTS: Significant reductions were observed ($p<0.05$) in weight (-5.79 ± 3.55 kg), waist circumference (-12.07 ± 5.56 cm), and percentage body fat (-2.43 ± 2.39%) compared to baseline values. In addition, subjects employing PGX had a significant reduction of 19.26 percent ($n=17$; $p<0.05$) and 25.51 percent ($n=16$; $p<0.05$) in total and LDL plasma cholesterol values, respectively, at the end of the study period. CONCLUSION: The consumption of PGX in concert with lifestyle modifications may be a useful strategy for weight loss in overweight and obese individuals.

(*Altern Med Rev* 2010;15(1):68-75)

Ronald G. Reichert, ND – Director of scientific affairs, Canadian Centre for Functional Medicine, Coquitlam, BC
Correspondence address: 1550 United Boulevard, Coquitlam, BC, Canada V3K 6Y2
Email: doctorreichert@functionalmedicine.ca

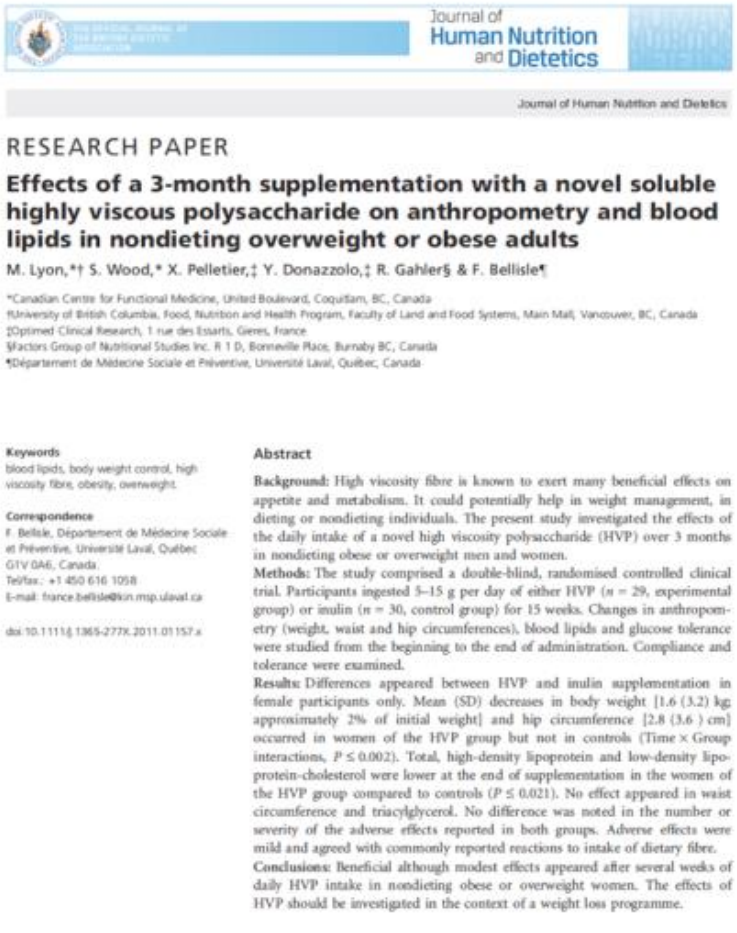
Michael R. Lyon, MD – Medical director, Canadian Centre for Functional Medicine, Coquitlam, BC; adjunct professor, University of British Columbia, Food, Nutrition, and Health Program, Vancouver, BC

### Introduction

According to recent data published by the World Health Organization, obesity has reached global epidemic proportions, with more than one billion adults affected by this chronic disorder.[1] Coronary artery disease, stroke, insulin resistance, metabolic syndrome, type 2 diabetes, hypertension, and cancer are well known medical co-morbidities associated with excess body weight.[2] In addition, a recent epidemiological study confirmed that adult obesity is associated with a significant reduction in life expectancy. This study estimates that 40-year old male and female nonsmokers lose an average 7.1 and 5.8 years of life, respectively, due to obesity.[3] A number of therapeutic interventions are available for the overweight/obese individual, including surgery, drug therapy, and lifestyle modifications such as diet and exercise.

The cornerstones of healthy weight management are changes in diet and exercise. Although the research relationship between diet and exercise has not been consistent,[4] a recent systematic review suggests a positive association.[5] The authors report that in overweight and obese individuals, diet (i.e., caloric restriction) in conjunction with exercise accounted for a significantly greater initial weight loss than diet intervention alone (-13 ± 9.6 kg versus -9.9 ± 9.6 kg, respectively). Moreover, those employing the combination therapy maintained a higher degree of weight loss (+20%) compared to those utilizing dietary measures alone after 12 months (-6.7 ± 8.3 versus -4.5 ± 11.3 kg, respectively).

# PGX Decreases Weight and Improves Blood Lipids



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RESEARCH PAPER

## Effects of a 3-month supplementation with a novel soluble highly viscous polysaccharide on anthropometry and blood lipids in nondieting overweight or obese adults

M. Lyon,*† S. Wood,* X. Pelletier,‡ Y. Donazzolo,‡ R. Gahler§ & F. Bellisle¶

*Canadian Centre for Functional Medicine, United Boulevard, Coquitlam, BC, Canada
†University of British Columbia, Food, Nutrition and Health Program, Faculty of Land and Food Systems, Main Mall, Vancouver, BC, Canada
‡Optimed Clinical Research, 1 rue des Essarts, Gieres, France
§Factors Group of Nutritional Studies Inc. R 1 D, Bonneville Place, Burnaby BC, Canada
¶Département de Médecine Sociale et Préventive, Université Laval, Québec, Canada

**Keywords**
blood lipids, body weight control, high viscosity fibre, obesity, overweight.

**Correspondence**
F. Bellisle, Département de Médecine Sociale et Préventive, Université Laval, Québec G1V 0A6, Canada.
Tel/fax.: +1 450 616 1058
E-mail: france.bellisle@kin.msp.ulaval.ca

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**Abstract**

**Background:** High viscosity fibre is known to exert many beneficial effects on appetite and metabolism. It could potentially help in weight management, in dieting or nondieting individuals. The present study investigated the effects of the daily intake of a novel high viscosity polysaccharide (HVP) over 3 months in nondieting obese or overweight men and women.

**Methods:** The study comprised a double-blind, randomised controlled clinical trial. Participants ingested 5–15 g per day of either HVP ($n = 29$, experimental group) or inulin ($n = 30$, control group) for 15 weeks. Changes in anthropometry (weight, waist and hip circumferences), blood lipids and glucose tolerance were studied from the beginning to the end of administration. Compliance and tolerance were examined.

**Results:** Differences appeared between HVP and inulin supplementation in female participants only. Mean (SD) decreases in body weight [1.6 (3.2) kg; approximately 2% of initial weight] and hip circumference [2.8 (3.6 ) cm] occurred in women of the HVP group but not in controls (Time × Group interactions, $P \leq 0.002$). Total, high-density lipoprotein and low-density lipoprotein-cholesterol were lower at the end of supplementation in the women of the HVP group compared to controls ($P \leq 0.021$). No effect appeared in waist circumference and triacylglycerol. No difference was noted in the number or severity of the adverse effects reported in both groups. Adverse effects were mild and agreed with commonly reported reactions to intake of dietary fibre.

**Conclusions:** Beneficial although modest effects appeared after several weeks of daily HVP intake in nondieting obese or overweight women. The effects of HVP should be investigated in the context of a weight loss programme.

# PGX Reduces Hepatic Steatosis in High-Sucrose-Fed Rats

Available online at www.sciencedirect.com
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Nutrition Research
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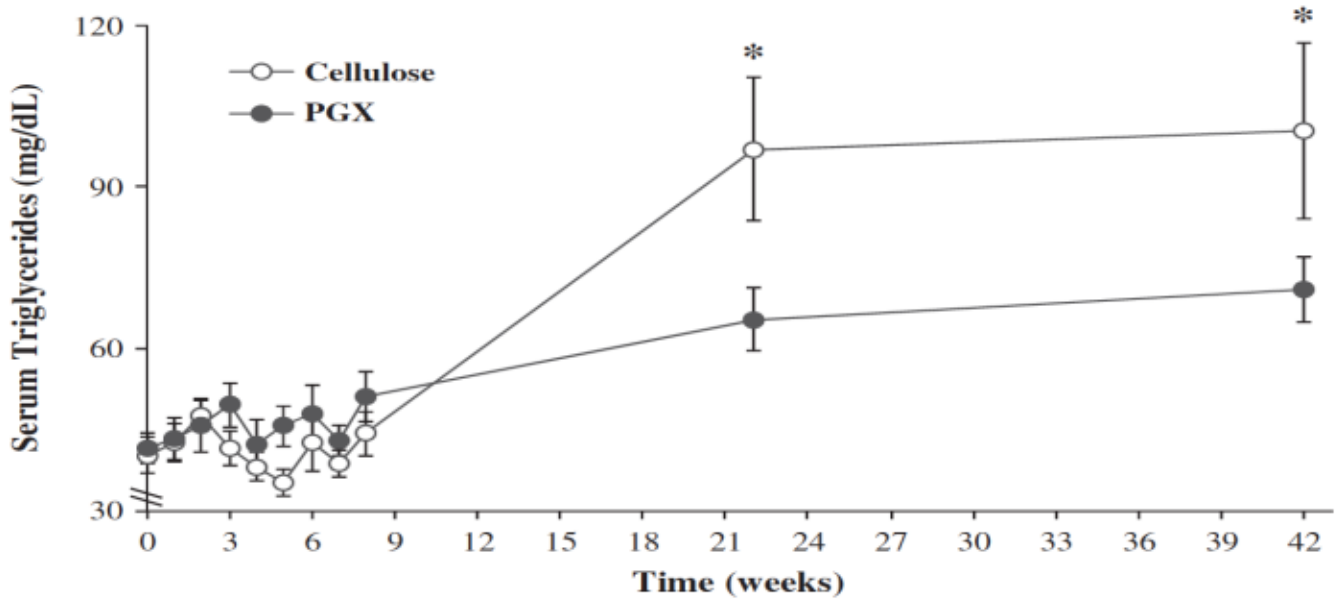
The soluble fiber complex PolyGlycopleX lowers serum triglycerides and reduces hepatic steatosis in high-sucrose-fed rats

Raylene A. Reimer[a,*], Gary J. Grover[b,c], Lee Koetzner[c], Roland J. Gahler[d],

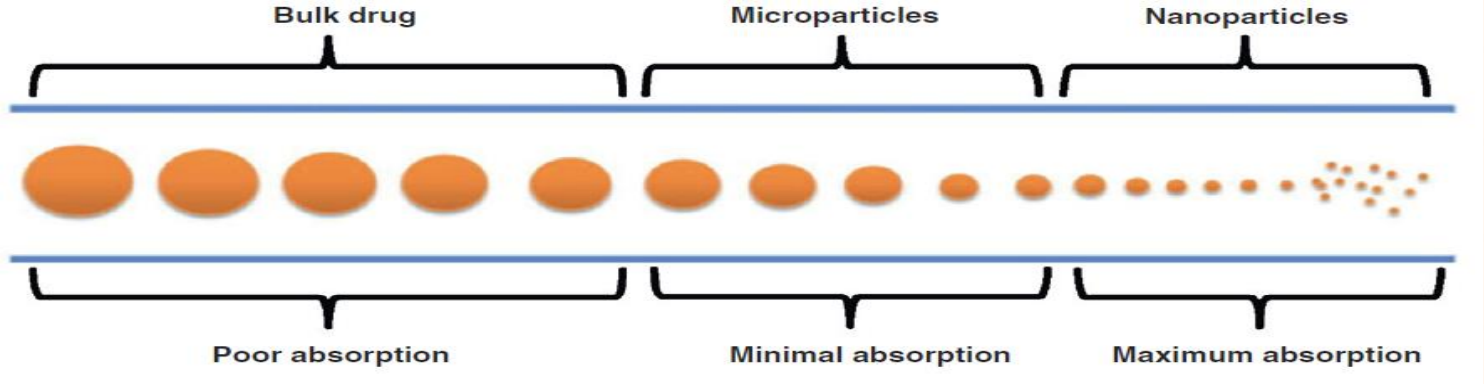


# PGX Provides Unique Benefits

- Reduces appetite and promotes effective weight loss
- Increases the level of compounds that promote satiety
- Decreases level of compounds that stimulate overeating
- Reduces the glycemic index of any food or beverage
- Increases insulin sensitivity
- Stabilizes blood sugar levels
- Lowers blood cholesterol and triglycerides

# Theracurmin-Pro 300

- Curcumin's benefit is limited by poor bioavailability



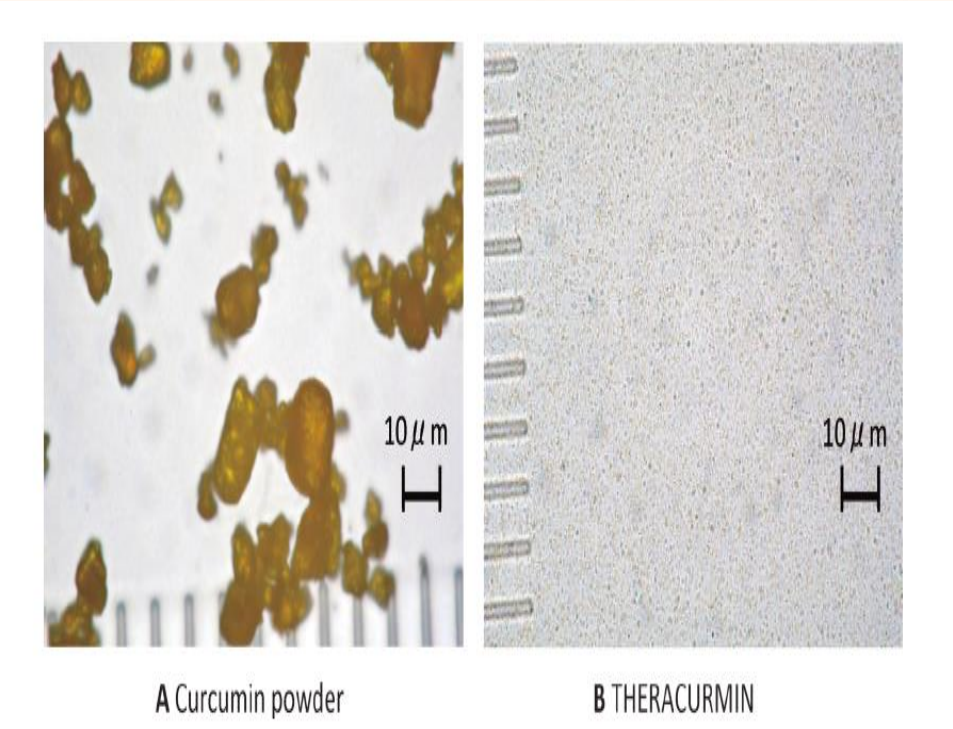

Yallapu 2012

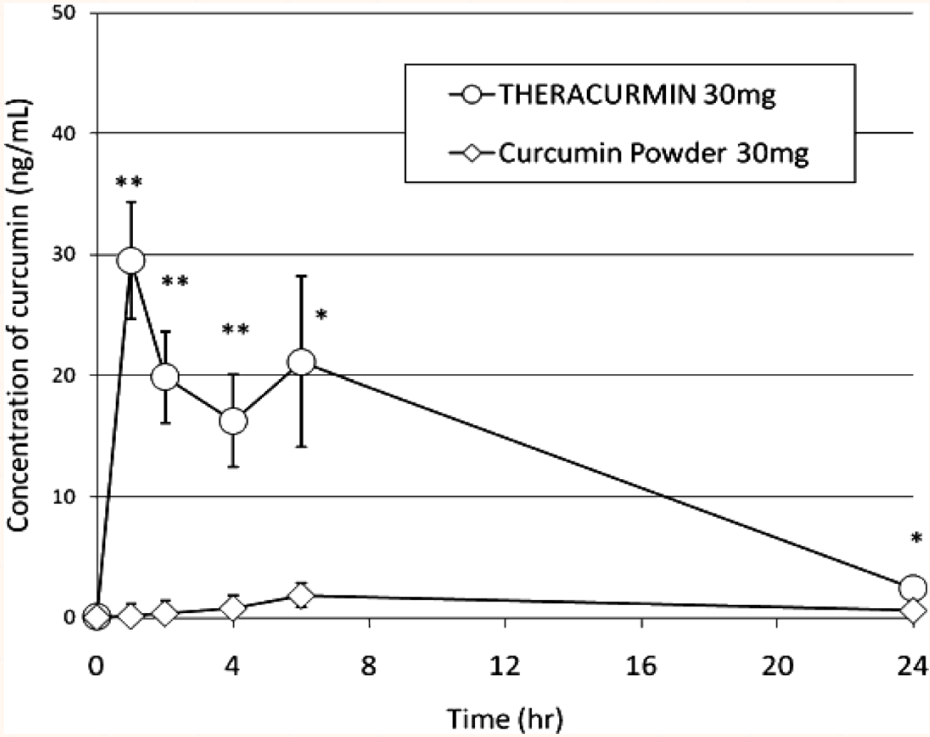
- Theracurmin-Pro 300
  - Much greater bioavailability than other forms of curcumin
  - 1st nanoparticle formulation available – reduced curcumin particle size 100-fold
  - Naturally emulsified – blood levels increase linearly with dose



Yallapu MM, et al. Curcumin nanoformulations: a future nanomedicine for cancer. Drug Discov Today. 2012 Jan;17(1-2):71-80.

# AUC of THERACURMIN 270-fold Higher Than Curcumin Powder in Humans






Sasaki H, et al. Innovative preparation of curcumin for improved oral bioavailability. Biol Pharm Bull. 2011;34(5):660-5.

# Summary

- Diabetes, pre-diabetes, and even normoglycemia on a spectrum rather than distinct categories
- Multiple contributing factors, including diet, lifestyle, and a growing influence of environmental factors, particularly POPs
- Lifestyle interventions highly effective for prevention/treatment of dysglycemia, without adverse effects associated with drug therapy
- Key nutrients, such as vitamin D, acetyl l-carnitine, PGX, and Theracurmin-Pro 300 address pathophysiology, effective for optimal glucose and insulin control