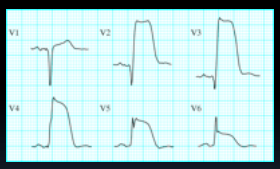
Developmental origins of disease

EVOLUTION OF DIABETES AND CARDIOVASCULAR DISEASE

Case

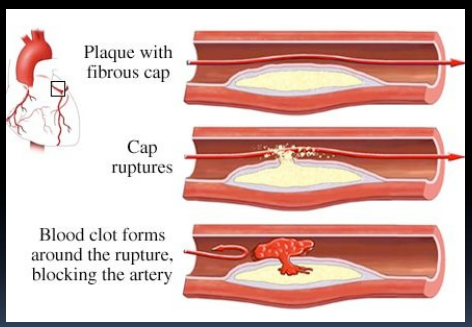
- 52 year old man comes to the ER complaining of chest pain, shortness of breath, sweating, and jaw tightness for the last 2 hours.
- He has a past medical history of hypertension, diabetes, high cholesterol, and a brother who had a triple bypass

Cardiovascular Disease



- Diabetes is a major risk factor for CVD
- Insulin resistance, diabetes, high lipids, hypertension, are associated with inflammatory state
- Why diabetes? Why heart attacks?

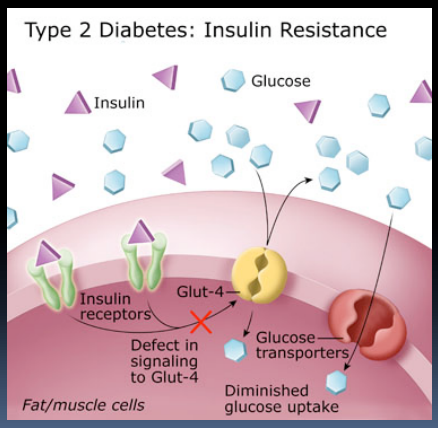
Atherosclerosis



- Lesion of strokes and heart attacks
- Inflammation causes plaques cause inflammation
- Pathogens found in plaques
- Ischemia reperfusion injury kills brain and heart cells

Diabetes

- Insulin resistance
- Decreased glucose uptake
- Hyperglycemia



Thrifty Genotype

- One of the earliest evolutionary medicine hypotheses
- Remember our discussion of Pima Indians?
- Some populations have astronomical rates of diabetes.

Imagine an island population

- Two kinds of people on the island –
  - Some are large and lean, little energy storage, more growth.
  - Others are smaller and with more adipose reserves, and less energy used for growth and maintenance.

Island Famine

- The second group might survive famine better, leaving more descendants
- Thrifty genotype
- Unpredictable food environment might select for thrifty genes
- May explain massive disparities in diabetes rates between different populations
- Genes that store fat and conserve energy. Insulin resistance.

Thriftiness of Insulin

- Insulin promotes storage of fat
- Insulin promotes storage of glucose in liver

- Insulin resistance means higher insulin levels
- Insulin resistance means less growth and less fuel for muscles

Overnutrition

- In adults obesity causes diabetes
- Gene-environment mismatch

- What about in infants?
  - birth weight was studied and an association with CVD was found.

Thrifty Phenotype

- Reported that developmental factors play a role
- Individuals with the same genes can end up following one of two pathways:
  - No intrauterine stress – plentiful nutrition – no insulin resistance
  - Stress, inadequate nutrition – insulin resistance

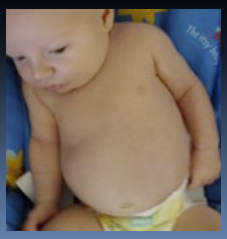
Developmental Origins of Adult Disease

- Risk of coronary disease correlates with BMI in adults
- Barker et al found opposite relationship in infants
- Diabetes has the same pattern – more in fatter adults, less in fatter infants

Abdominal Fat…

Fetal Undernutrition - Small Babies

- In response to poor nutrition, babies reduce their growth rate
- Stress induces other changes in physiology:
  - Lipid profile
  - Glucose metabolism
  - Blood pressure
  - Visceral fat storage



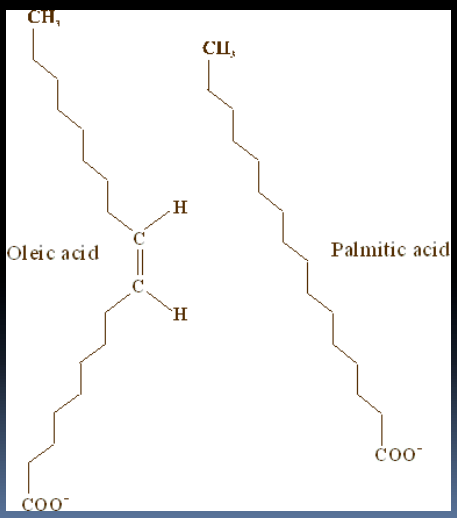
2 kinds of fat

Subcutaneous fat

- Mobilized slower
- Unsaturated free fatty acids

Visceral Fat

- Mobilized quicker
- **Fuel for brain**
- Saturated (with H) free fatty acids (no double bonds)
- Pro-inflammatory

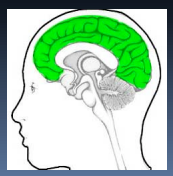


Visceral fat – Free fatty acids

- Human babies have big brains
- Unlike muscles, the brain has fixed metabolic needs
- In nutritional stress, the brain needs fuel

Visceral fat and Insulin resistance

- IR makes growth slow and increases glucose available for the brain
- Visceral fat mobilization causes FFA release
- So in stressed and underfed infants/children the brain gets the fuel that it needs.



Small for Gestational Age

- Preferentially deposit fat in visceral depot
- Short term energy balance
- Innervated by sympathetic nervous system
- Increased ability to respond to stress and to mobilize resources

Metabolic Syndrome

- In addition to insulin resistance:
- Increased levels of free fatty acids
- Impaired relaxation of blood vessels
- Increased catecholamines (adrenalin)
- Increased storage of visceral fat
  - Saturated free fatty acids also provide fuel for the brain
  - Visceral fat can be mobilized much faster than subcutaneous fat

Fetus senses environment

- Nutritional stress in utero
- Activates a "switch" that turns on insulin resistant/visceral fat phenotype
- Thrifty phenotype gamble
- Nutrient poor environment - no diabetes, no cardiovascular disease

Diseases of Western Civilization?

- May represent a thrifty phenotype bad gamble
- Increasing rates of diabetes hypertension in developing world
- Smaller the infant the higher rate of later diabetes, inflammation, cardiovascular disease

Big brains are human specific

- How can we test the hypothesis that insulin resistance and visceral fat metabolism are adaptations that protect the brain?

Tradeoffs

- Energy is finite
- Physiology and metabolism trade-offs

- What is the major source of mortality for small babies/toddlers?

Undernourished children die from infections

- Most childhood deaths are from infectious diarrhea
- Peak in early infancy and at age 2
- In traditional societies, age 2 is time of weaning – breast milk cannot keep up with demand. Undernourished children are at high risk of death at this time.

American Journal of Clinical Nutrition, Vol. 80, No. 1, 193-198, July 2004

Another benefit for insulin resistance?

- Blood glucose levels are higher
- Less glucose is metabolized by muscles, bone, and most growing tissues
- Some cells in the body are not dependant on insulin to metabolize glucose.
  - Brain
  - ***White blood cells***

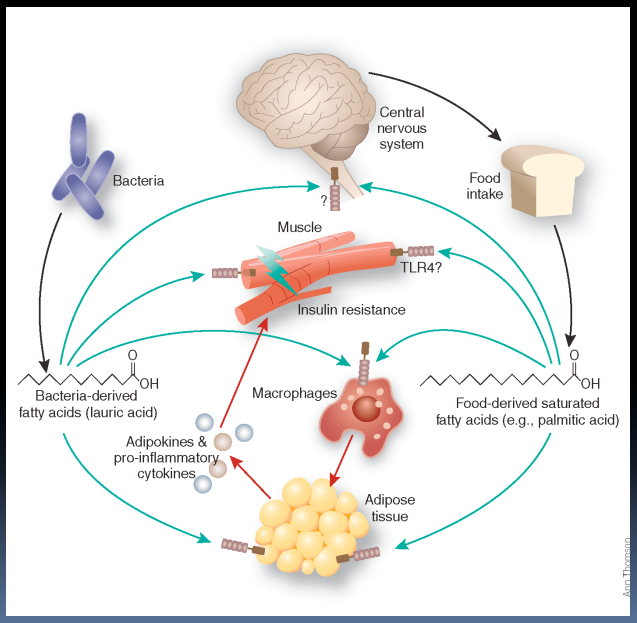
Resource Allocation

- Immune cells
  - In times of stress and infection, metabolic requirements of white blood cells skyrockets
  - Do not require insulin dependent glucose shunt
- Insulin resistance has the effect of delivering more fuel to the immune system
- Perhaps insulin resistance is promotes survival of undernourished children from diarrhea.

Short term vs Long term effects

- Short term – mild insulin resistance may help body fend off infection
- Long term – becomes full blown diabetes
- Immune function in diabetics is impaired and death from infection is increased!
- May be example of antagonistic pleiotropy

Why



Summary

- Thrifty genotype
- Thrifty phenotype
- Preservation of brain development
- Resistance to infection
- Mimicry
- Antagonistic Pleiotropy