

# UNDERSTANDING OBESITY AS A DISEASE

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# Disclosures

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App developer : “Guía interactiva para perder peso”

The patient is a 48 y.o woman with history of type 2 DM since age 35. Currently her hemoglobin A1c is 9.6 and she is being treated with a combination of metformin, glyburide and pioglitazone; she takes metoprolol for HTN and, last year, she was started on gabapentin for bilateral neuropathy. She follows a 1800 cal ADA, exercises 1 hour 5x Week, combining Zumba and other aerobic routines. She is showing progressive hypomenorrhea and her weight, currently 155 lbs, is increasing. She is 5 feet tall, BMI 30.3

## What would you do next?

- a) start insulin therapy to get her Hba1c at goal.
- b) discontinue glyburide, gabapentin, pioglitazone and metoprolol.
- c) refer her to a weight loss specialist.
- d) tell her to change her diet to 1500 cal and change her exercise program to 2 hours instead of 1.
- e) refer her to Surgery for gastric bypass.

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What is obesity?

True statements about obesity include all of the following, except:

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1. Body mass index  $>30$ .
2. Increase in body fat that is making the person sick.
3. Excessive fat that causes hormonal, mechanical and psychological illness.
4. Chronic, inflammatory, relapsing multifactorial disease.

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Before this obesity was considered a behavioral disorder, where the patient was overeating an

Missing last part of statement

# Obesity Medicine Association

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“Obesity is defined as a **chronic, relapsing, multi-factorial, neurobehavioral disease** wherein an **increase in body fat** promotes **adipose tissue dysfunction** and abnormal fat mass physical forces resulting in **adverse metabolic, biomechanical, and psychosocial health consequences.**”

<http://obesitymedicine.org/obesity-algorithm/>





# Disease

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- Incorrect function of organ, part, structure or system of the body.
- Results from genetic, developmental errors, infection, poisons, nutritional deficiency or imbalance, toxicity or unfavorable environmental factors.
- Manifests as illness, sickness.

# How is adiposity accurately measured?

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- a) Body mass index.
- b) Bioelectric impedance.
- c) Underwater body weight.
- d) DEXA scan.

# Indirect methods

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## Body Mass Index

- Adolphe Quetelet, 1832.
- Indirect way to measure adiposity.
- Low cost.
- Reproducible.
- No gender or racial distinction.

$$\text{BMI} = \frac{\text{weight (lb)} * 703}{\text{height}^2 (\text{in}^2)}$$

OR

$$\text{BMI} = \frac{\text{weight (kg)}}{\text{height}^2 (\text{m}^2)} \quad (\text{metric})$$

# Indirect Methods

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## Anthropometric measures

- Waist circumference.
- Waist/hip ratio.
- Neck circumference.
- Are reproducible, low cost, consider gender differences.



# Indirect Methods

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## Bioelectric impedance

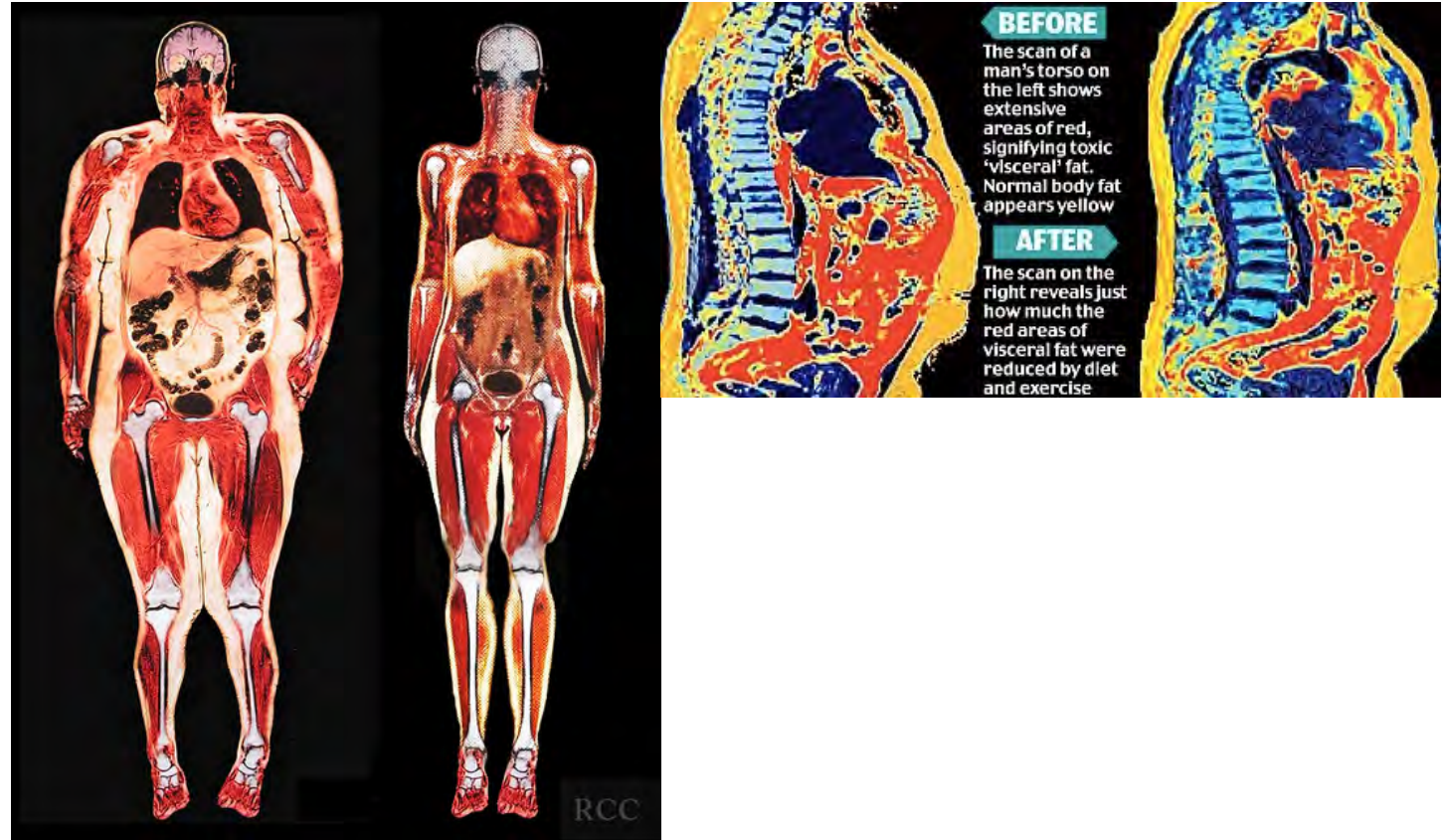
- Small electric current travels through body and calculates amount of fat.
- Relative low cost.
- Accuracy depends on level of hydration.



# Direct Methods

## Dexa, CT or MRI scans

- very accurate.
- expensive, limits its use.



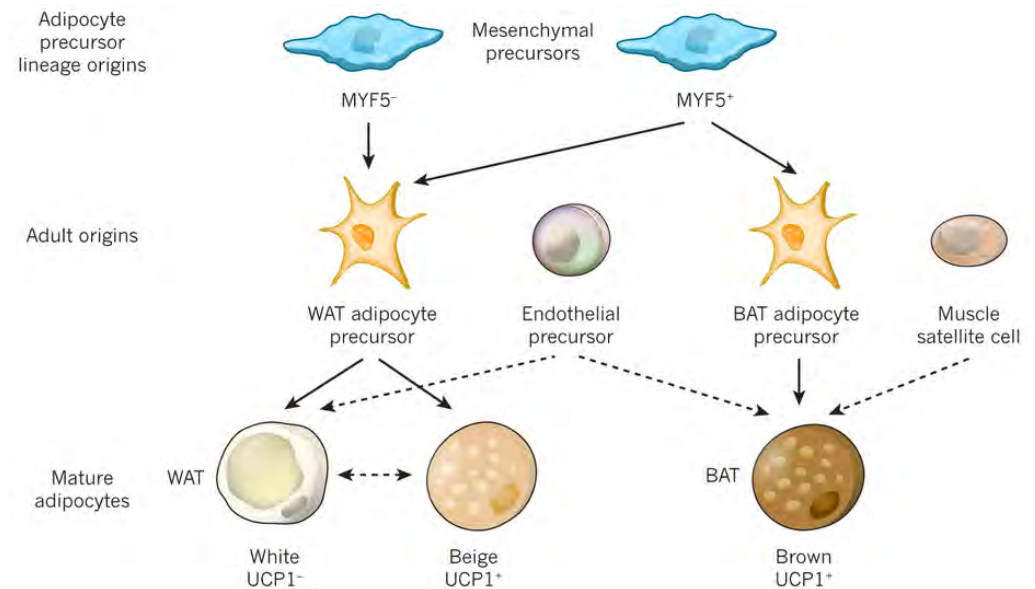
# Functions of the adipocyte are?

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- A) fat storage.
- B) thermogenesis.
- C) appetite regulation, glucose and lipid metabolism.
- D) A and B.
- E) all of the above.

# Types of adipocytes

- White adipose tissue (WAT) (visceral)
  - fat storage
  - hormone secretion
- Brown adipose tissue (BAT)
  - high in mitochondria
  - thermogenesis (UCP1-thermogenin)
- Beige



Peirce V, Carobbio S, Vidal-Puig A.

Nature. 2014 Jun 5;510(7503):76-83. doi: 10.1038/nature13477. Review.



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What causes obesity?

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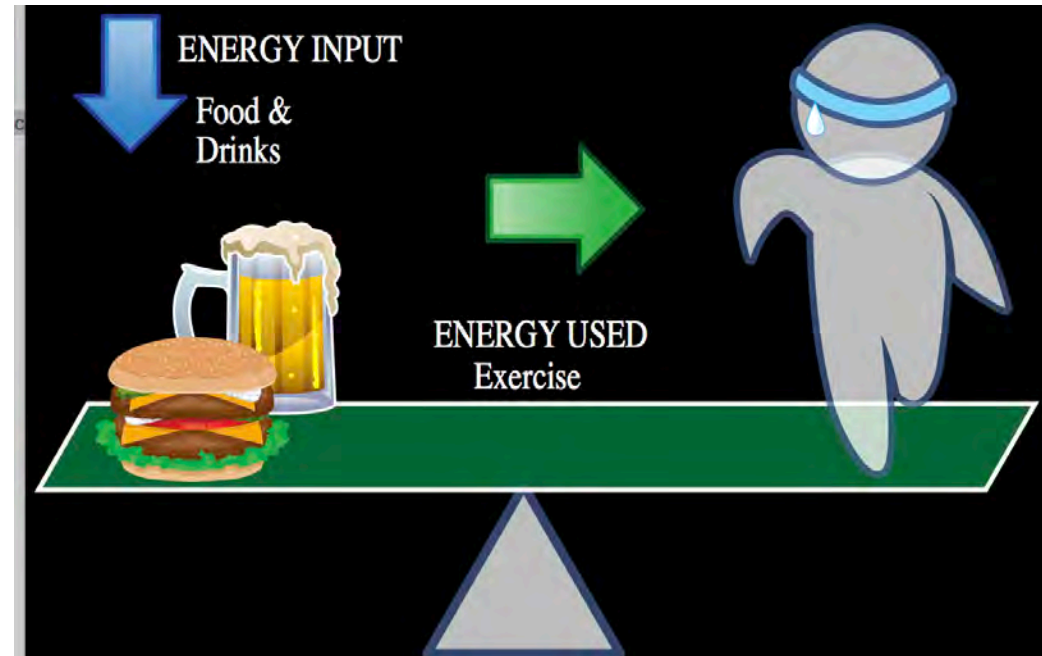
“A mind is like a  
parachute. It  
doesn't work  
unless it is open.”

Frank Zappa



# The energy balance theory

- Law of conservation of energy:
  - In an closed system, energy cannot be created or destroyed.
- Calories in calories out.
- Does not fully explain why isocaloric diets have different outcomes.
- **Calories are not the only variable.**



Obesity and energy balance: is the tail wagging the dog?

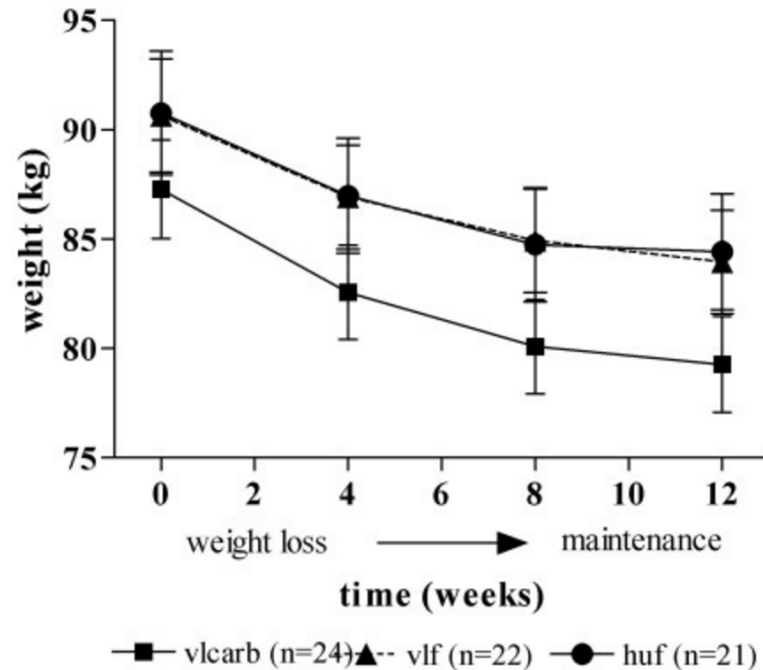
Wells JC, Siervo M.

Eur J Clin Nutr. 2011 Nov;65(11):1173-89. doi: 10.1038/ejcn.2011.132. Epub 2011 Jul 20. Review.

# Comparison of isocaloric VLCarb, VLF and HUF on body composition and cardiovascular risk

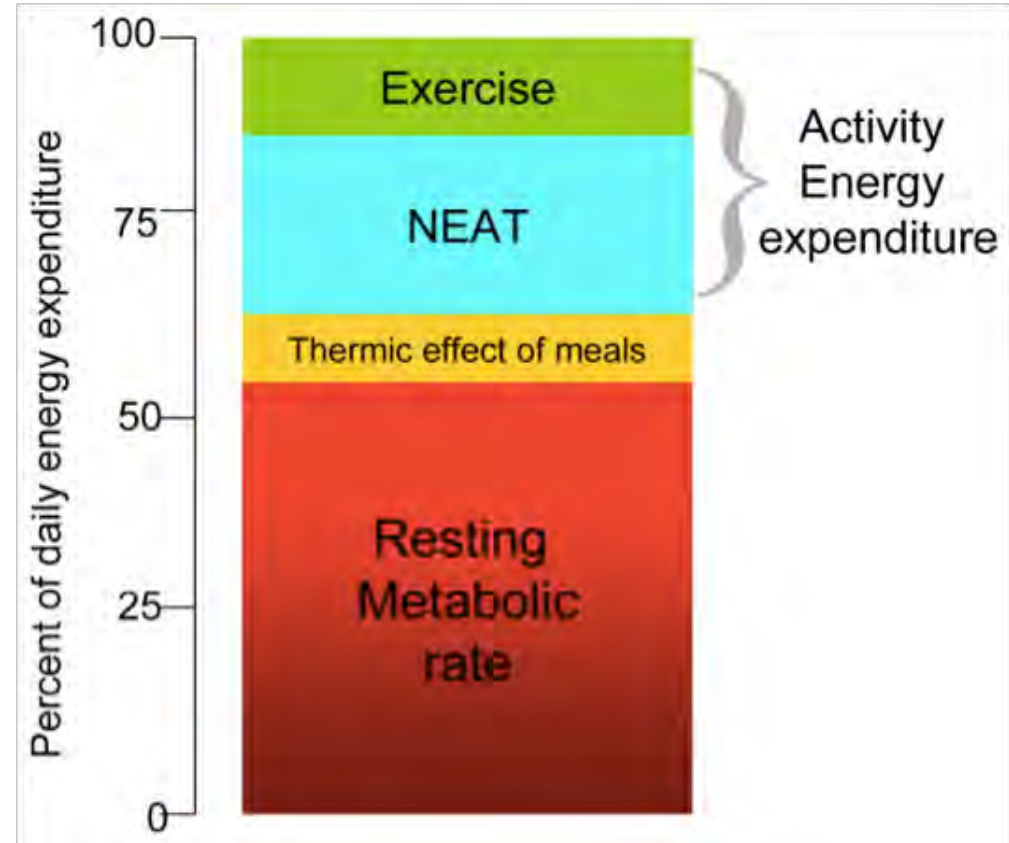
## Conclusion

Isocaloric VLCARB results in similar fat loss than diets low in saturated fat, but are more effective in improving TG, HDL-C, fasting and post prandial glucose and insulin concentrations.



# Energy expenditure

- Basic metabolic rate (BMR) 65-70%
- Thermic effect of food (TEF) 5-10%
- Non exercise activity thermogenesis (NEAT) 10-15%
- Exercise (E) 5-10%

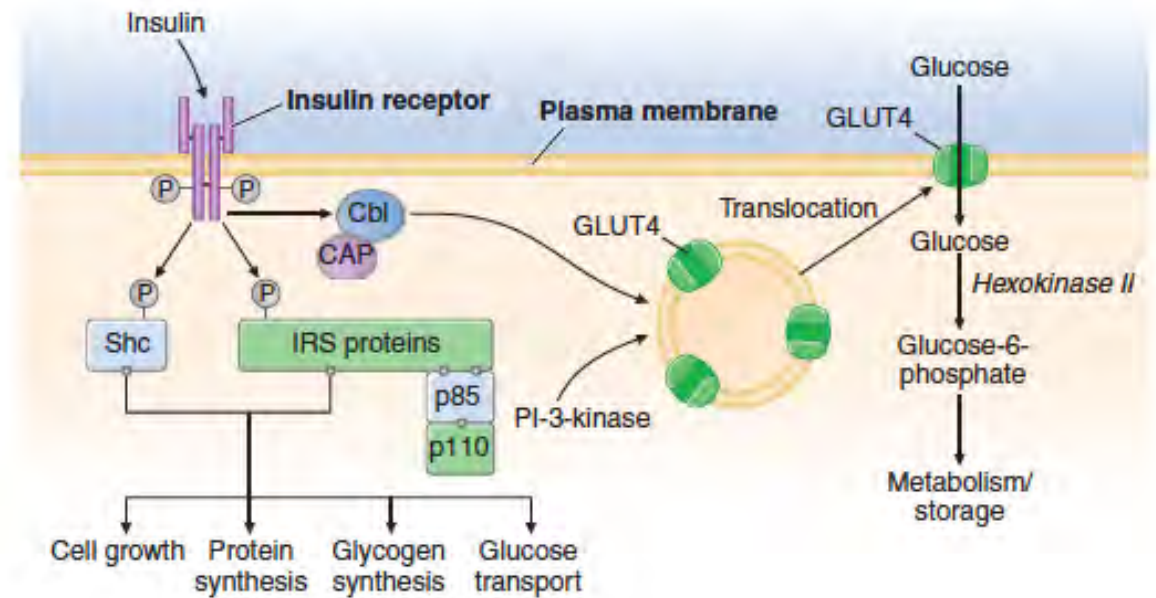


Nonexercise activity thermogenesis—liberating the life-force.  
J Intern Med. 2007 Sep;262(3):273-87



# Insulin

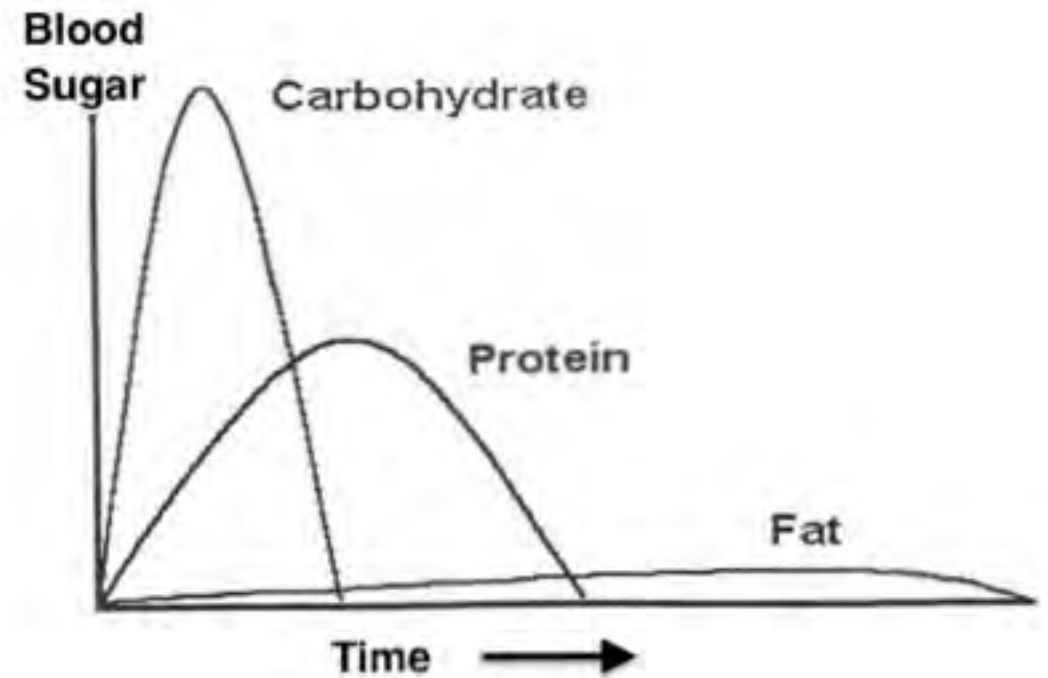
- Master hormone of fat storage.
- Stimulates lipogenesis.
- Inhibits lipolysis.
- Stimulates protein synthesis.
- Stimulates glycogen formation.



# Insulin

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- Both carbohydrates and proteins stimulate release of insulin.
- Fat has less impact on insulin release.

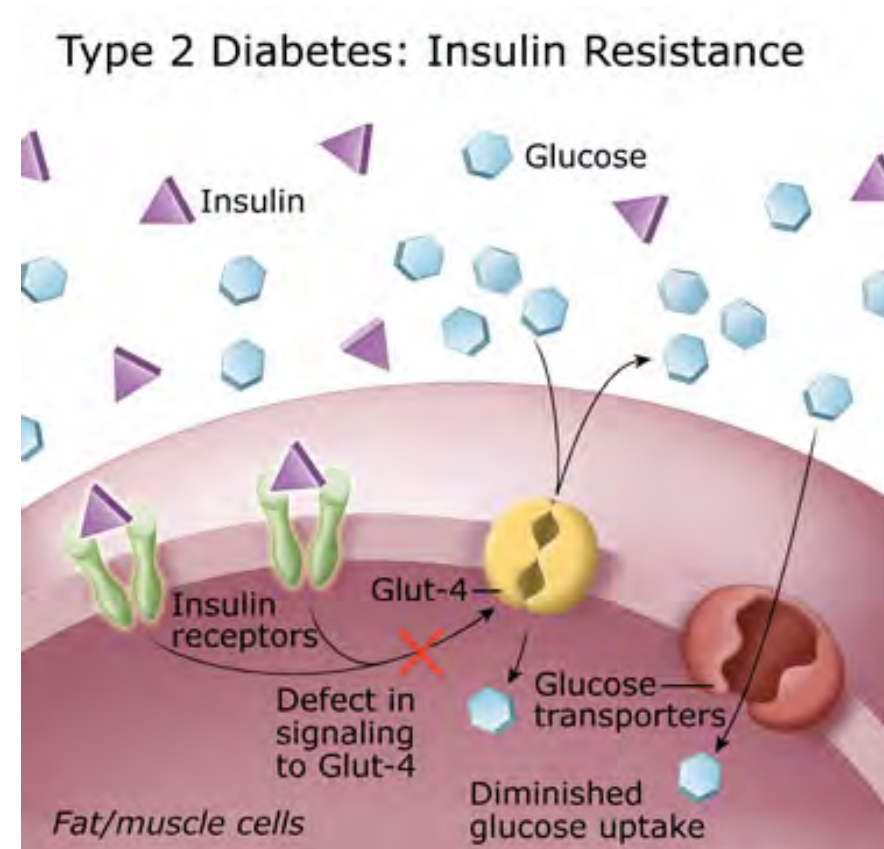




# Insulin Resistance

- Defined clinically as the inability of a known quantity of exogenous or endogenous insulin to increase glucose uptake and utilization in an individual as compared to a normal population

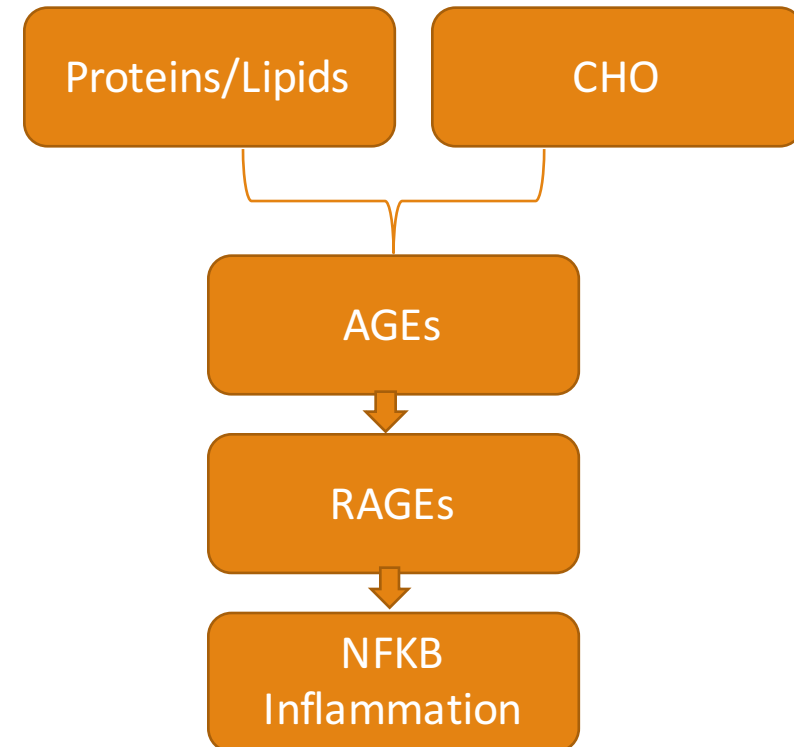
Exp Clin Endocrinol Diabetes 2001; 109(Suppl 2): S135-S148  
DOI: 10.1055/s-2001-18576



# Advance glycation end products (AGEs)

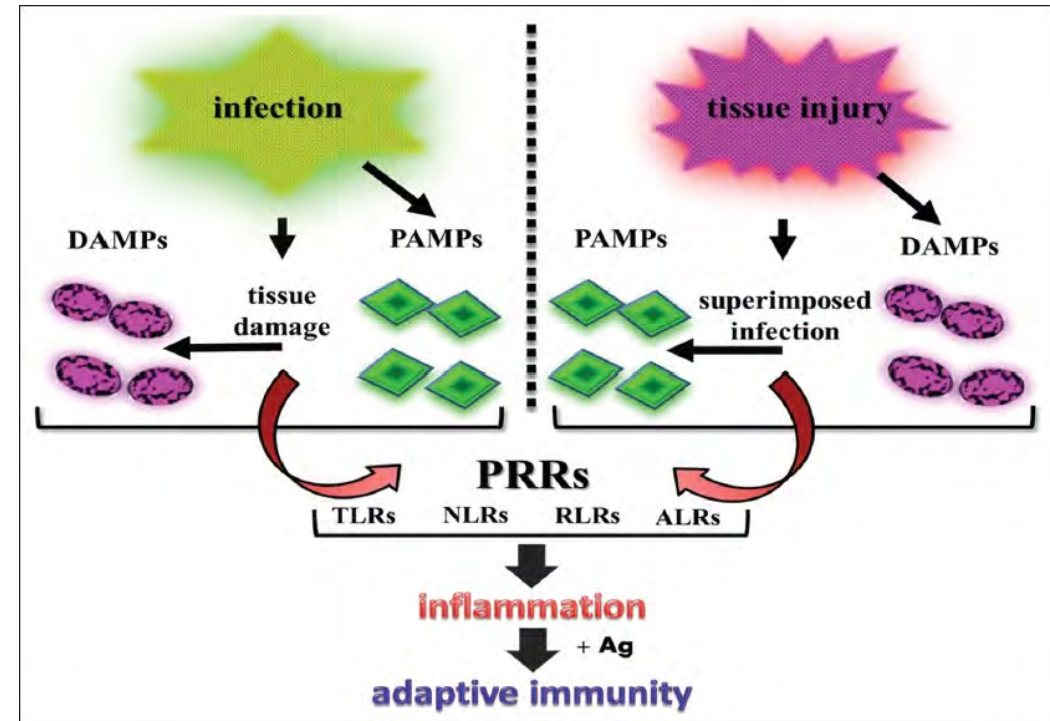
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- **Proteins or lipids that become glycated as a result of exposure to sugars.**
- **Hyperglycemia causes AGEs even in non diabetics.**
- **Also can be generated by high temperature cooking (enhances flavor).**
- **Can come from ingested food.**
- **They generate ROS and induce inflammation.**
- **Receptor for AGE (RAGEs) (PRR)**



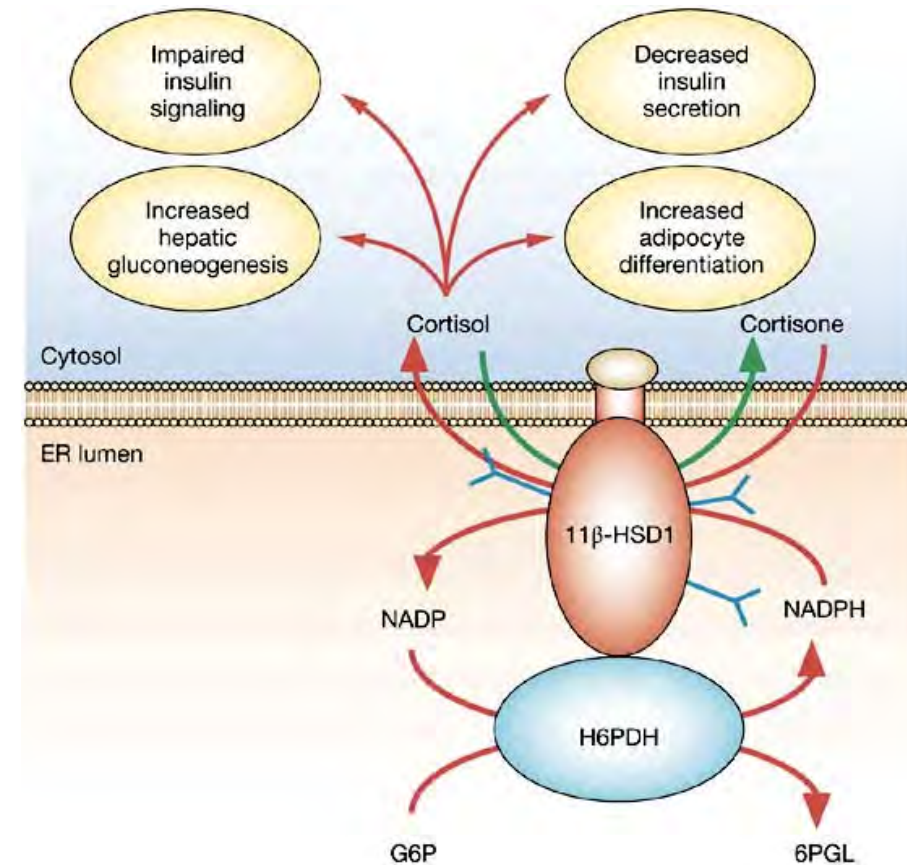
# Food can cause inflammation

- Pattern recognition receptors (PRRs)
  - Toll like receptors (TLR).
  - NOD like receptor (NLR).
  - Retinoid acid inducible gene (RIG) like receptor.
  - C Type Lecithin Receptors (CLRs).
  - Absence in melanoma 2 like receptors (ALRs)
- Pathogen-associated molecular patterns (PAMPs) LPS-mannose.
- Damage-associated molecular patterns (DAMPs) Amylin, Glucose, FFAs.



# Cortisol

- Stress hormone.
- Increases blood glucose (gluconeogenesis).
- Promotes insulin resistance.
- Increases adipocyte differentiation.
- Increases visceral fat.



Selective inhibition of 11 $\beta$ -hydroxysteroid dehydrogenase type 1 as a novel treatment for the metabolic syndrome  
Tomlinson Nature Clinical Practice Endocrinology & Metabolism (2005) 1, 92-99

# Circadian rhythm alterations

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Decreased amount of sleep and altered day/night cycles are associated with:

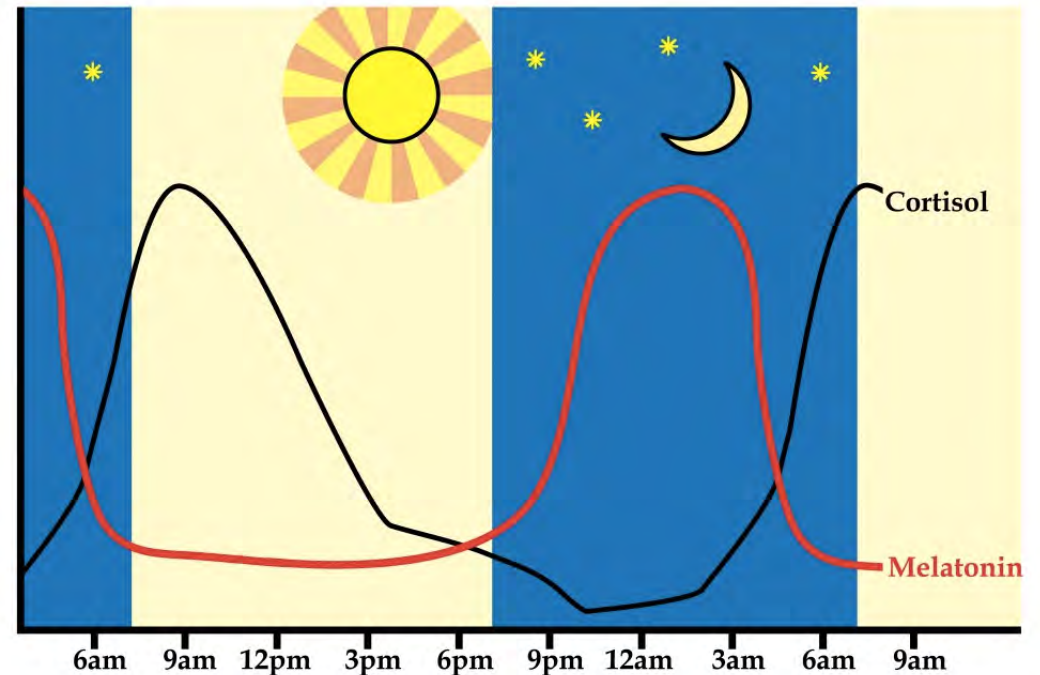
- Elevated Ghrelin (hunger).
- Leptin.....
- IL-6 (inflammation).
- Food cravings (especially CHO).
- Increased post prandial glucose.
- Insulin resistance.



Taheri S, Short Sleep Duration Is Associated with Reduced Leptin, Elevated Ghrelin, and Increased Body Mass Index. Froguel P, ed. *PLoS Medicine*. 2004;1(3):e62.

# Circadian rhythm alterations

- Shift workers are predisposed to metabolic disorders and cancers.
- Circadian regulation of hormones, cortisol and melatonin balance.
- Blue light suppresses melatonin release.





# Endocrine disrupting chemicals (EDCs)

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- Exogenous chemical substances that may bind to endocrine receptors and can stimulate, inhibit or prevent the binding of the natural hormone.
- Also called obesogens.
- May increase the number or size of adipocytes.
- May lower BMR.

ARE  
**Obesogens**  
MAKING  
US FAT?



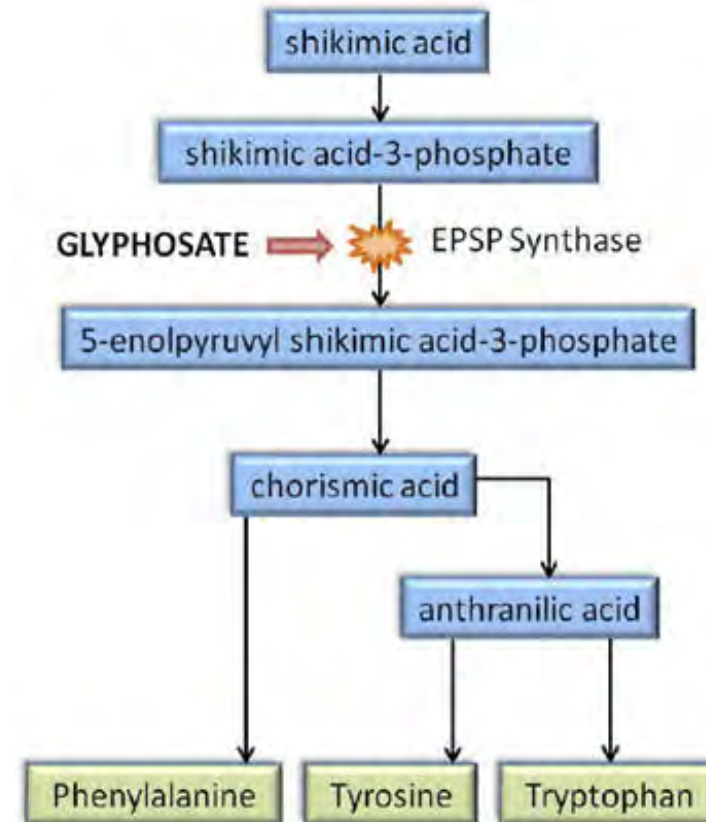
# Endocrine disrupting chemicals (EDCs)

EDCs	Effect
Tobacco	Increases IR (50% Obesity in offspring)
Polycyclic Aromatic Hydrocarbons ( PAHs)	Increases visceral fat / Inflammation
Tributyltin (TBT)	Increase Adipogenesis (PPAR-γ)
Bisphenol A (BPA)	Estrogenic / Dopamine addictive behavior
Flame Retardants	Increase Adipogenesis Insulin resistance / Thyroid Dysfunction
Polychlorinated Biphenyls (PCBs)	Disrupt Thyroid Function
Phthalates	Increase Adipogenesis
Perfluorinated Chemicals (PFCs)	Increases Insulin and Leptin levels
Glyphosate	Disruption of Gut Bacteria (dysbiosis)



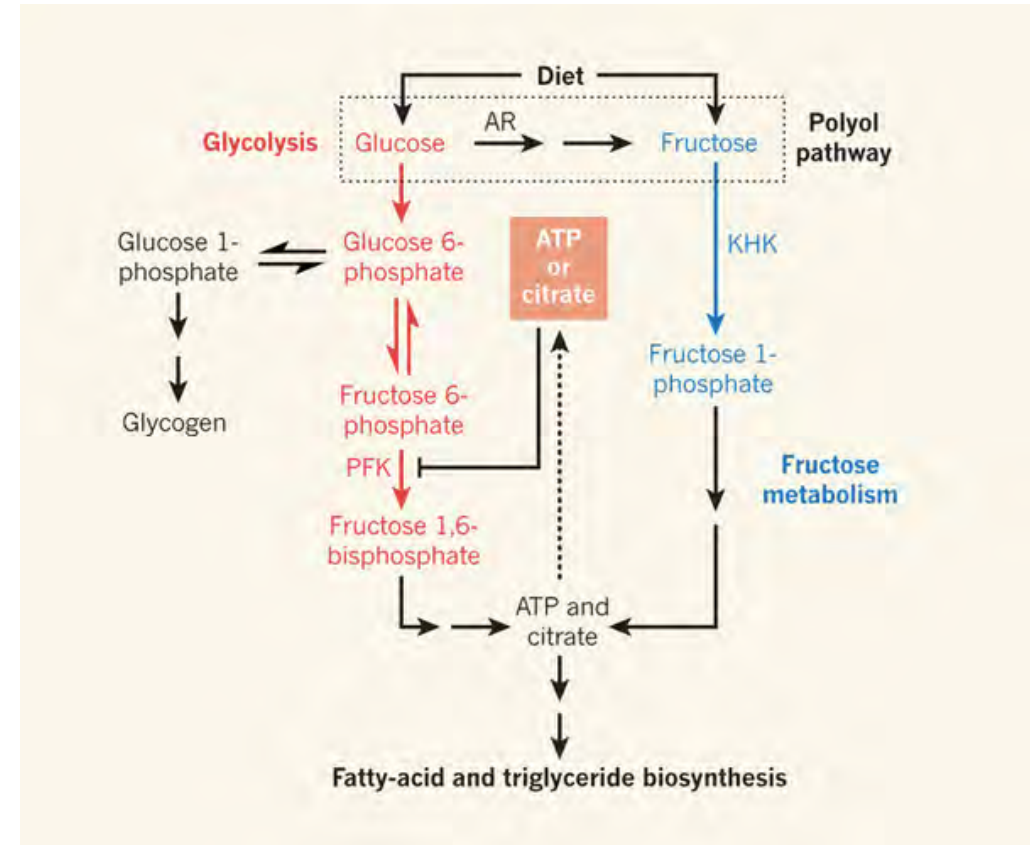
# Glyphosate

- Mineral chelation (Cu, Zn, Mn, Mg).
- Toxic to soil microorganisms.
- Decreases beneficial bacteria in soil.
- Increases fusarium sp. and pathogenic bacteria, including salmonella sp., C. botulinum, pseudomonas sp.
- Decreases rhizobia, enterococci.



# Fructose: the “devil”

- Has a low glycemic index.
- Can only be metabolized by the liver.
- Could lead to fatty liver and NASH.
- Highly addictive.
- FFAs will lead to further insulin resistance.
- Increases uric acid production, increasing BP contributing to the metabolic syndrome.
- ?????????? Correct last point.



Metabolic syndrome; Costas A  
Nature 502, 181–182 (10 October 2013)

Fructose: it is  
“alcohol without  
the buzz”



Robert Lustig MD, American Society for Nutrition. Adv. Nutr. 4: 226–235, 2013;

# Artificial sweeteners and food additives

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- Artificial sweeteners are likely to cause weight gain (adiposity).
- May increase risk of type 2 DM, promoting insulin resistance.
- Effects are likely related to the alteration in the microbiota.
- Food emulsifiers also disrupt the microbiota (soy lecithin).
- Monosodium glutamate (MSG) increases insulin secretion.



# Nutritional deficiency

- Obesity is a chronic inflammatory disorder that depletes the body of nutrients, causing malnutrition.
- The lack of nutrients further impairs insulin signaling and predisposes to type 2 DM.

TABLE 1: Prevalence of micronutrient deficiencies in obesity and diabetes [5, 6, 46, 58–61].

Micronutrient	Prevalence of deficiency	
	Obesity	Type 2 diabetes
Thiamine B1	15–29%	17–79% <sup>a</sup>
Pyridoxine B6	0–11%	—
Cobalamin B12	3–8%	22%
Folic Acid	3–4%	—
Ascorbic acid C	35–45%	— <sup>b</sup>
Vitamin A	17%	—
Vitamin D	80–90% <sup>c</sup>	85–90% <sup>c</sup>
Vitamin E	0%	0%
Zinc	14–30%	—
Chromium	—	20–40%
Selenium	58%	—

—Prevalence data not available

<sup>a</sup>Data includes type 1 diabetic patients

<sup>b</sup>Decreased levels of ascorbic acid have been reported in diabetes

<sup>c</sup>Prevalence reflects rates vitamin D insufficiency.

Nutrient	Effect
Vitamin D	B Cell function / IR
Chromium	Enhances insulin signal / IR
Biotin	Hexokinase, hepatic uptake of glucose /IR
Thiamine	Glycolysis, TCA / def increase AGEs
Magnesium	Enhances insulin Signal /IR
Selenium	Insulin mimetic effect
Zinc	Insulin mimetic effect – Cell division

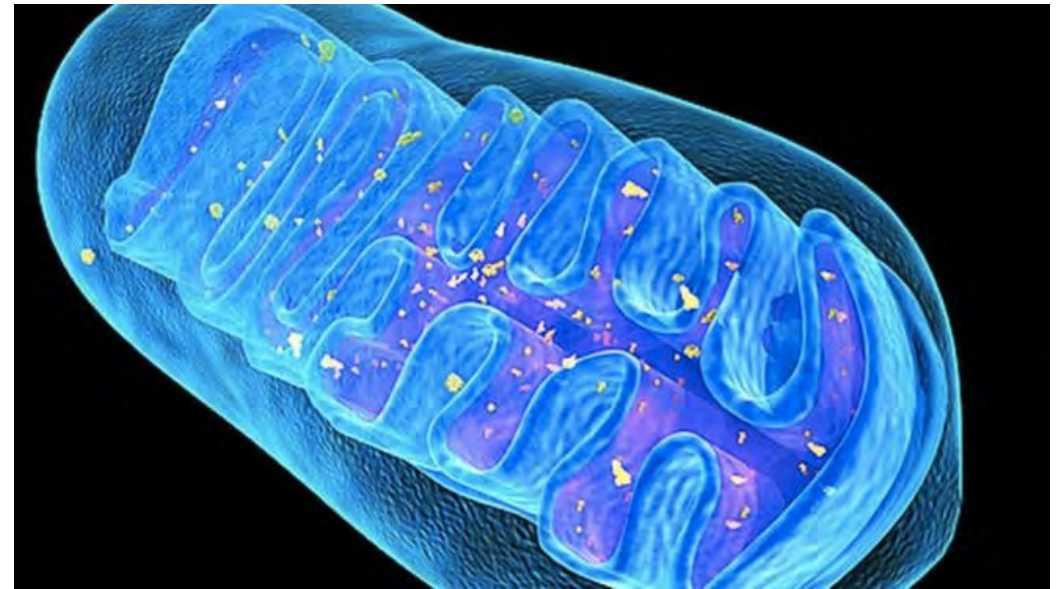
Via M. The Malnutrition of Obesity: Micronutrient Deficiencies That Promote Diabetes. *ISRN Endocrinology*. 2012;2012:103472. doi:10.5402/2012/103472.



# Mitochondrial Dysfunction

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- Mitochondrias convert nutrients into ATP.
- Mitochondrias decline with age. (in function, number or both?)
- Fat accumulation increases with age due to decreased fat oxidation.
- Glucose oxidation increases ROS.
- Fat Oxidation decreases ROS.
- Proper nutrition is required for normal function.
- First statement is incorrect.



How do you increase  
the number of  
mitochondrias ?



# AMPK upregulation

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- Fasting.
- Muscular strength exercises.
- Low glucose diet.
- Hypoxia.
- Cold exposure.
- Near-infrared light.



Is obesity  
iatrogenic?

# The following medications are associated with weight gain, except:

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- a) Insulin.
- b) Sulfonylureas.
- c) Beta blockers.
- d) Antihistaminics.
- e) Exenatide .
- f) SSRIs.

# Medications that cause or worsen fat accumulation

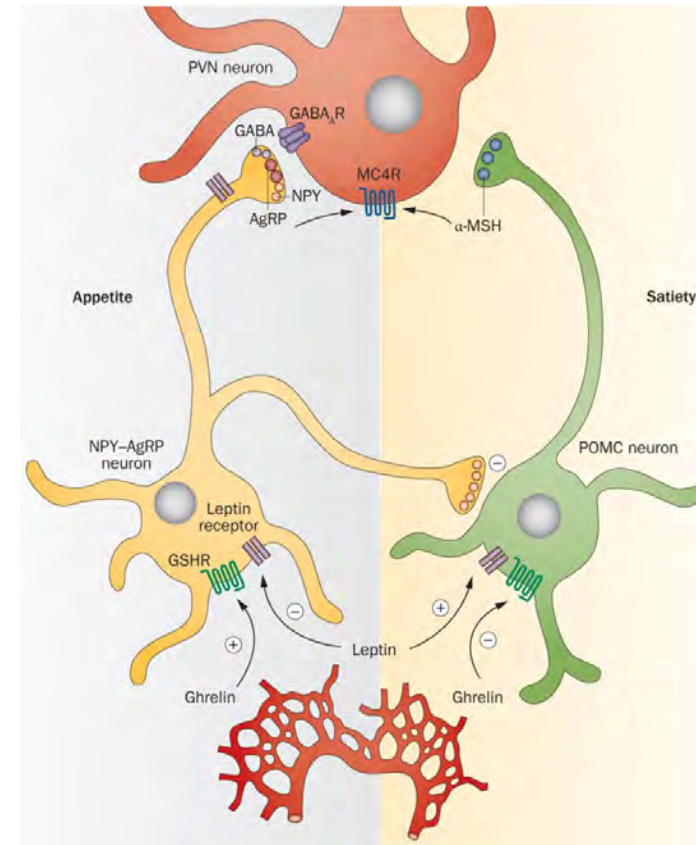
Drug	Possible mechanism
Insulin	Worsens insulin resistance
Sulfonylureas	Increases the release of insulin
TZDs	PPAR $\gamma$ , increases Lipogenesis
Beta blockers	B3R, decreases BMR 10%
SSRIs, Fluoxetine, Paroxetine,	Unknown
Steroids	Increases blood sugars
Xenoestrogen's and Progestin's	Hormonal disruption
Statins	Insulin Resistance
PPIs	Alteration on the microbiome
THC	Increases appetite
HCTZ	Insulin Resistance

# Medications that cause or worsen fat accumulation

Drug	Possible mechanism
TCA Amitriptyline, Doxepin, Nortriptyline Mirtazapine	Unknown
Antipsychotics Lithium, Haloperidol, risperidone, olanzapine	Unknown
H1 antagonists Cetirizine, Fexofenadine	Unknown
MAOi Selegiline, Phenzelzine	Unknown
Antiepileptic drugs Valproic Acid, Carbamazepine, Gabapentin,	Unknown

# Appetite regulation and weight gain

- Hypothalamic (ARC) control of appetite.
- Orexigenic pathway (Hunger-POMC).
- Anorexigenic pathway (Satiety-NPY-AgRP).
- Multiple systems involved: pancreas, gut, brain.
- System feedback mechanism inhibited by food:
  - fat (CCK)
  - carbs ( Insulin/Leptin)
  - proteins (GLP1/PP)



# Genetics of Obesity

5% of obesity is attributable to genetic defects

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- most common genetic abnormality is a defect on the melanocortin receptor 4 (MCR4).
- leptin and leptin receptor defects.
- POMC mutations.
- Prader-Willy syndrome (hypotonia - hyperphagia).
- Bardet–Biedl syndrome (RP-polydactyly)

Young age, hyperphagia



Farooqi IS (2006) The severely obese patient—a genetic work-up  
*Nat Clin Pract Endocrinol Metabol* 2: 172–177 doi:10.1038/ncpendmet0137

# Epigenetics of Obesity

- Inheritable and reversible phenomena that affect gene expression without altering the underlying base pair sequence resulting from environmental influence.
- DNA methylation, histone modification and chromatin remodeling are influenced by diet.
- Intrauterine malnutrition predisposes to obesity and diabetes in the offspring (transgenerational).

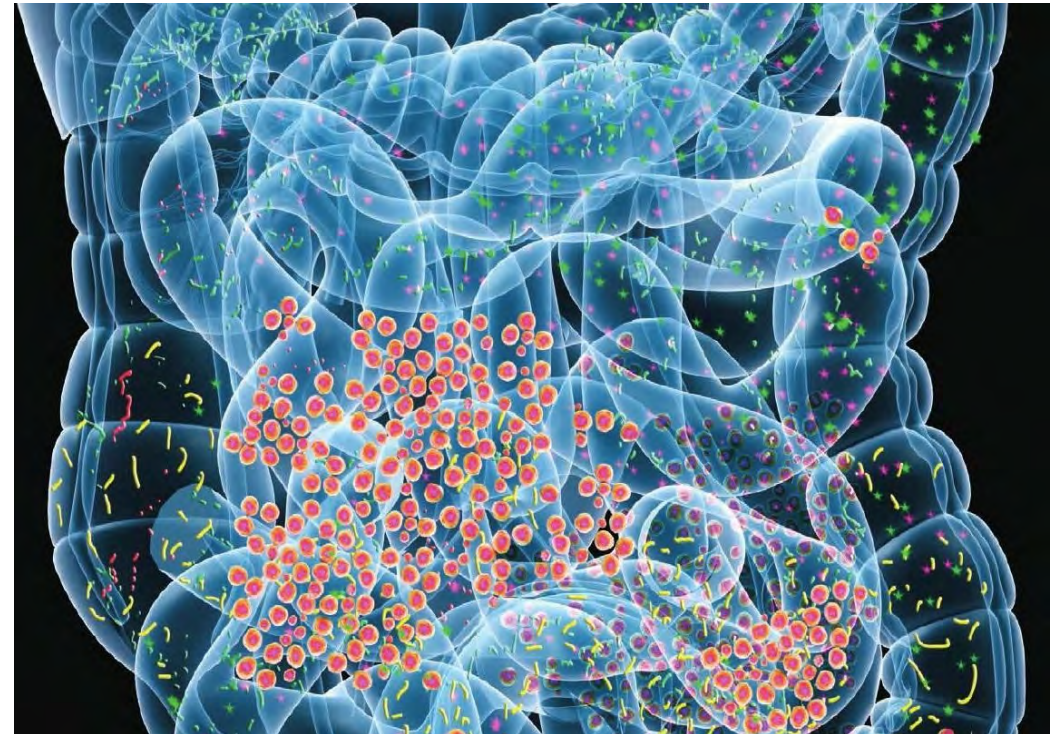




Are your gut  
bacteria making  
you fat?

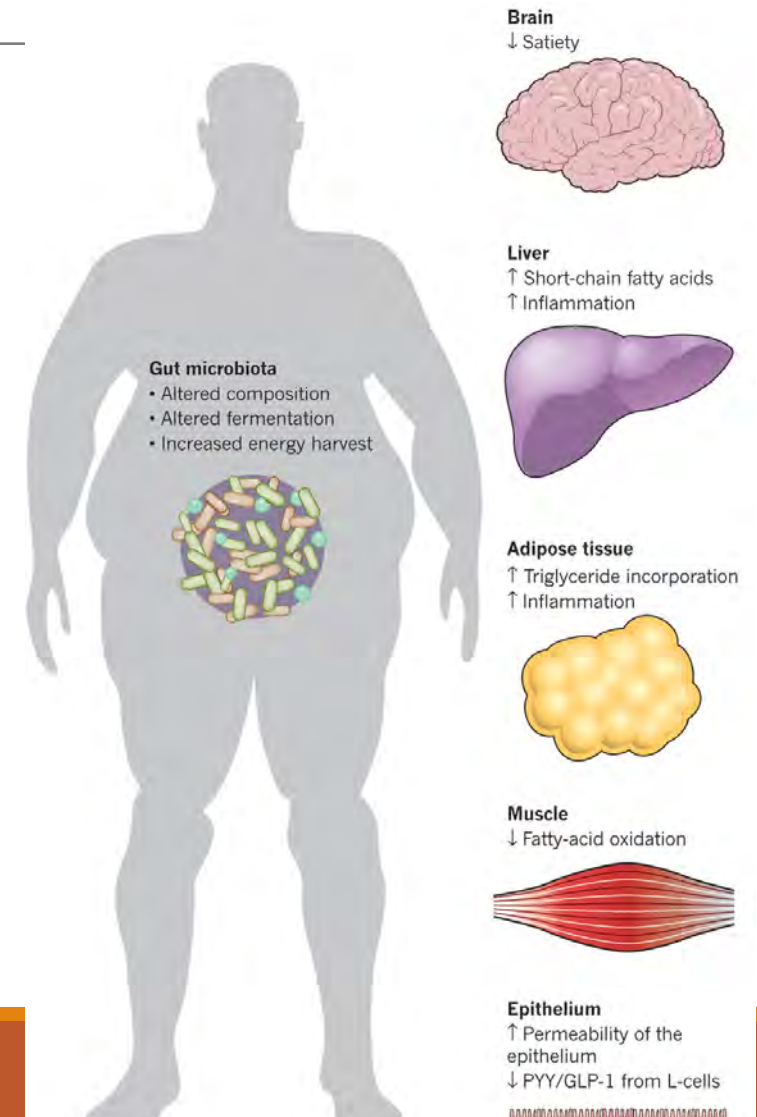
# Microbiota and obesity

- 100 trillion bacteria.
- >1000 species.
- 90% firmicutes and Bacteroidetes (?????)
  - Actinobacteria
- Diet alters the microbiome.
- Prebiotics ( food for the microbiota) fiber–RS.
- Probiotics (alive microorganisms).
- Symbiotics ( pre and probiotics).
- Brain gut axis, gut-liver axis.



# Microbiota and Obesity

- Modulation of the inflammatory response.
- Fiber → SCFA → GLP-1 / Inflammation.
- Formation of secondary bile acids
  - lipid metabolism
- GLP-2 ↓ intestinal permeability / endotoxemia.
- Endocannabinoid system.
- Fasting-induced adipose factor (ANGPTL4)
  - Inhibits LPL ( hypertriglyceridemia)



Lean Gut Microbiota	Obese Gut Mibrobiota
Normal ratio of Firmicutes / Bacteriodetes More Diversity	Increased Firmicutes Less Diversity
Normal Satiety (↑GLP-1-PYY)	Less Satiety (↓GLP-1-PYY)
Decreased fecal SCFA	Increased fecal SCFAs (Propionate)
↑AMPK / Fat Oxidation Increased FIAF	↓ AMPK / Fat Oxidation Decreased FIAF (Lipogenesis)
↑ Insulin Sensitivity	↓ Insulin sensitivity
↓ Inflammation (LPS)	↑ Inflammation (LPS)
↑ Butyric Acid	↓ Butyric Acid

## **What would you do next?**

- a) start insulin therapy to get her Hba1c at goal, discontinue glyburide, gabapentin, pioglitazone and metoprolol.**
- b) refer her to a weight loss specialist.**
- c) tell her to lower her diet to 1500 cal and make her exercise 2 hours instead of 1.**
- d) refer her to Surgery for gastric bypass.**

This patient has a chronic inflammatory process that is causing her to store fat while she is unable to use fat that she has already stored. It is also causing her more inflammation, likely from a disrupted microbiome due to poor dietary choices, lack of sleep, hormonal dysregulation and epigenetic mediated factors.

Changing her medications would likely help her to loose weight.



# The Horizon .....

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The food and beverage industry spends approximately \$2 billion per year marketing to children.

The fast food industry spends more than \$5 million every day marketing unhealthy foods to children.

Nearly 40% of children's diets come from added sugars and unhealthy fats.

Kids watch an average of over ten food-related ads every day (nearly 4,000/year).



# Take home points

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- It is detrimental for patient care to assume that patients eat too much and lack the willpower to exercise.
- We are barely beginning to understand the complexity of the human body and its interaction with the a toxic environment, including the microbiome.
- Iatrogenic obesity plays a big role in the persistence of the disease.
- Get motivated, learn more about obesity.

