# Insulin Resistance: Explanations and Treatment Approaches

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# No disclosures

# Objectives

As a result of completing this training, participants will be able to:

- Describe the roles of insulin action
- Describe factors that impair insulin action
- Describe strategies to improve insulin action

# Outline

- Intro to clinical case
- Part 1: Definition of insulin resistance
  - Review of insulin signaling
  - Measuring insulin resistance
  - Signs and symptoms of insulin resistance
- Part 2: Factors that impair insulin action including obesity, fatty liver, and glucocorticoids
- Part 3: Strategies to improve insulin action
  - Diet, exercise, pharmacologic (metformin, GLP-1 agonists), bariatric surgery
- Wrap-up of clinical case

# Case: Christine

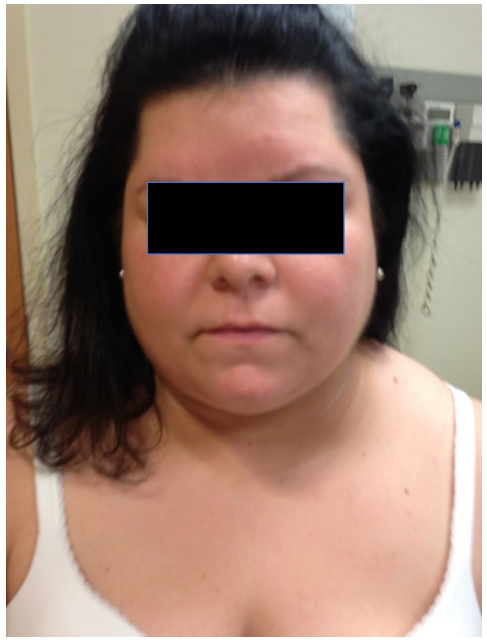
- 38 year old woman presents for improved glucose management
- She is hoping to attempt to get pregnant
- She has had poorly controlled type 2 diabetes for 10 years
- PMH:
  - Infertility
  - Polycystic ovarian syndrome (PCOS)
  - Obesity

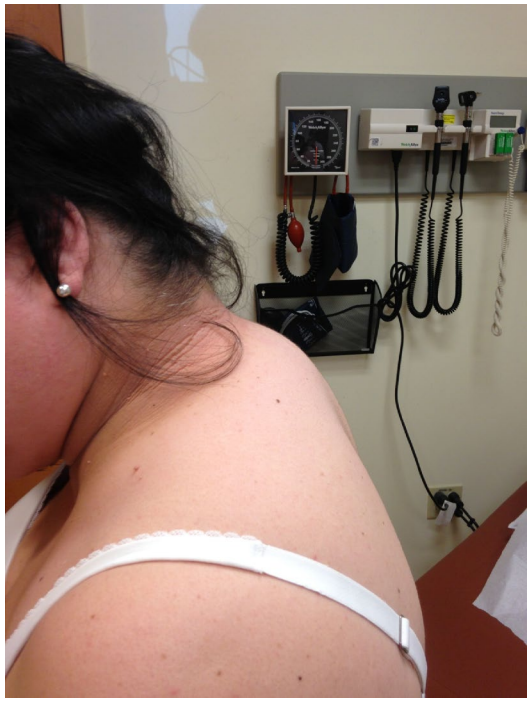
# Case: Christine

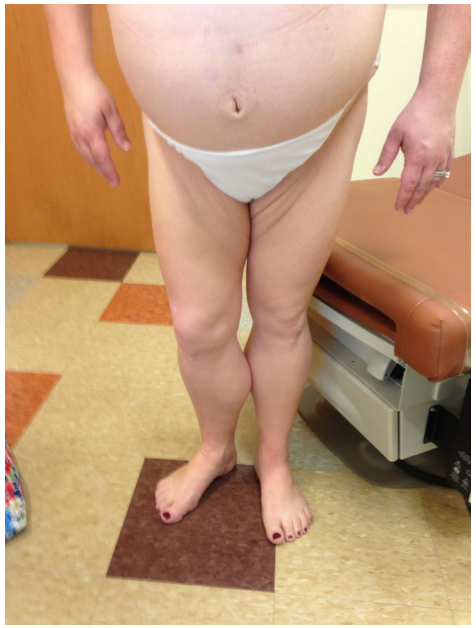
- Family History positive for diabetes
- Current management
  - Metformin 1 gram bid
  - NPH insulin 20 units in the morning, 100 units in the evening
  - Insulin aspart 60 units with meals
  - (3.3 units of insulin/kg of body weight)
- Labs
  - Hemoglobin A1c 8.5%
  - Total testosterone 98 ng/dL (nl to 48)
  - Lipids: TC 197 mg/dL, Trig 240 mg/dL (nl to 150), LDL 77 mg/dL (nl to 129), HDL 36 mg/dL (nl 40-80)
  - AST 39 IU/L (nl to 30), ALT 60 IU/L (nl to 52)
- No cortisol excess, no CAH (21 hydroxylase deficiency)

# Physical exam

BMI 33
Wt 202 lbs







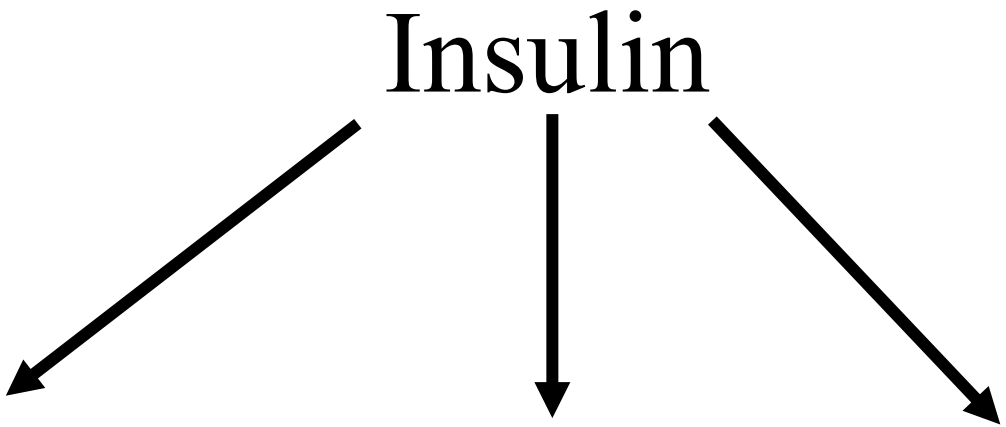
# Part 1: What is insulin resistance?

- “Lack of response of blood sugar in the face of adequate amount of insulin”

  Yalow and Berson JCI 1960

- Impaired insulin action on whole-body glucose uptake
- Classic tissues for insulin action:
  - Liver
  - Muscle
  - Fat

# Overview of Insulin Function




**MUSCLE**

*Transports glucose, amino acids and ions*

*(K &phos)*

**LIVER**

*inhibits glucose production*

*allows glycogen storage*

**ADIPOCYTE**

*Forms triglycerides to store fat*

*inhibits lipolysis*

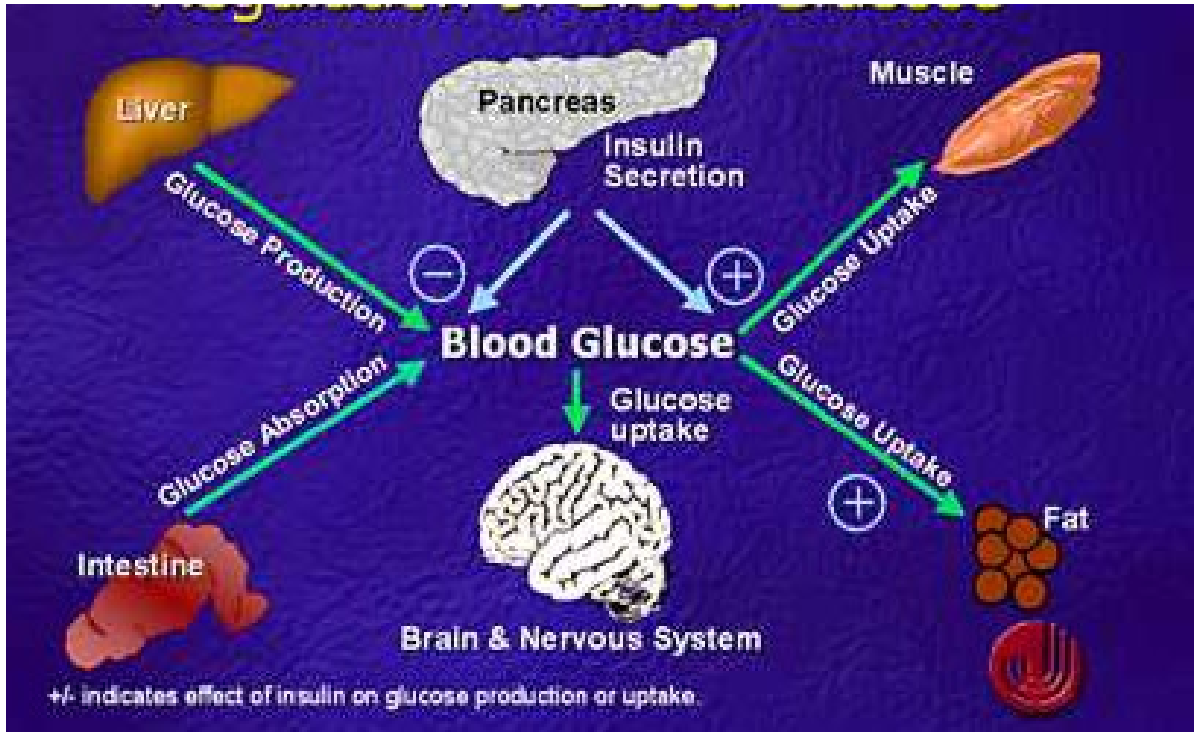
Consequences of insulin resistance:

- Increased muscle breakdown
- Increased gluconeogenesis, glycogenolysis
- Increased lipolysis

*Modified and reproduced with permission McDonnell ME. Hyperglycemic emergencies, Boston Medical Center Fellows Lecture Series 2013*

# IR: Friend or Foe ?

- Insulin resistance in muscle, liver, and fat allows for nutrients to flow to brain and immune tissues
- This is **adaptive** in states of physiologic stress
  - Infection
  - Starvation
- This is **not adaptive** in times of nutrient excess
  - Obesity
  - Diabetes
  - Hyperlipidemia

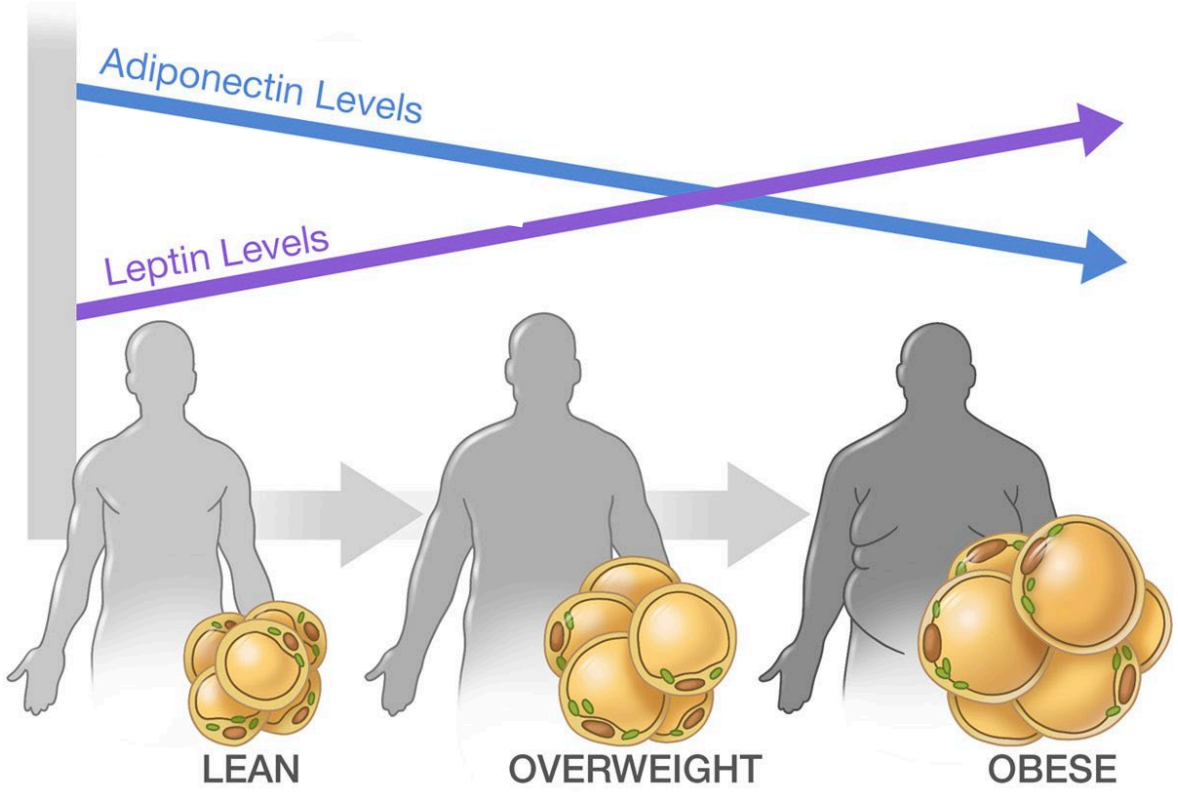





From Richard Beaser ; Evolution of Diabetes Therapy, Medscape 2009

# Insulin Action and Adiponectin

- Visceral adipose tissue secretes a plasma protein called adiponectin
- Adiponectin decreases insulin resistance and increases tissue fat oxidation, resulting in lower circulating fatty acid levels
- Leptin is a protein that circulates in proportion to fat mass



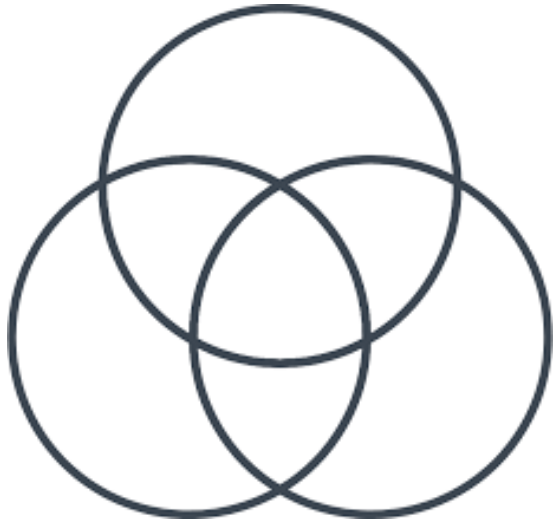

Adapted from: Shangang Zhao. Circulation Research. Adiponectin, Leptin and Cardiovascular Disorders, Volume: 128, Issue: 1, Pages: 136-149, DOI: (10.1161/CIRCRESAHA.120.314458)

# Can Insulin Resistance Be Measured?

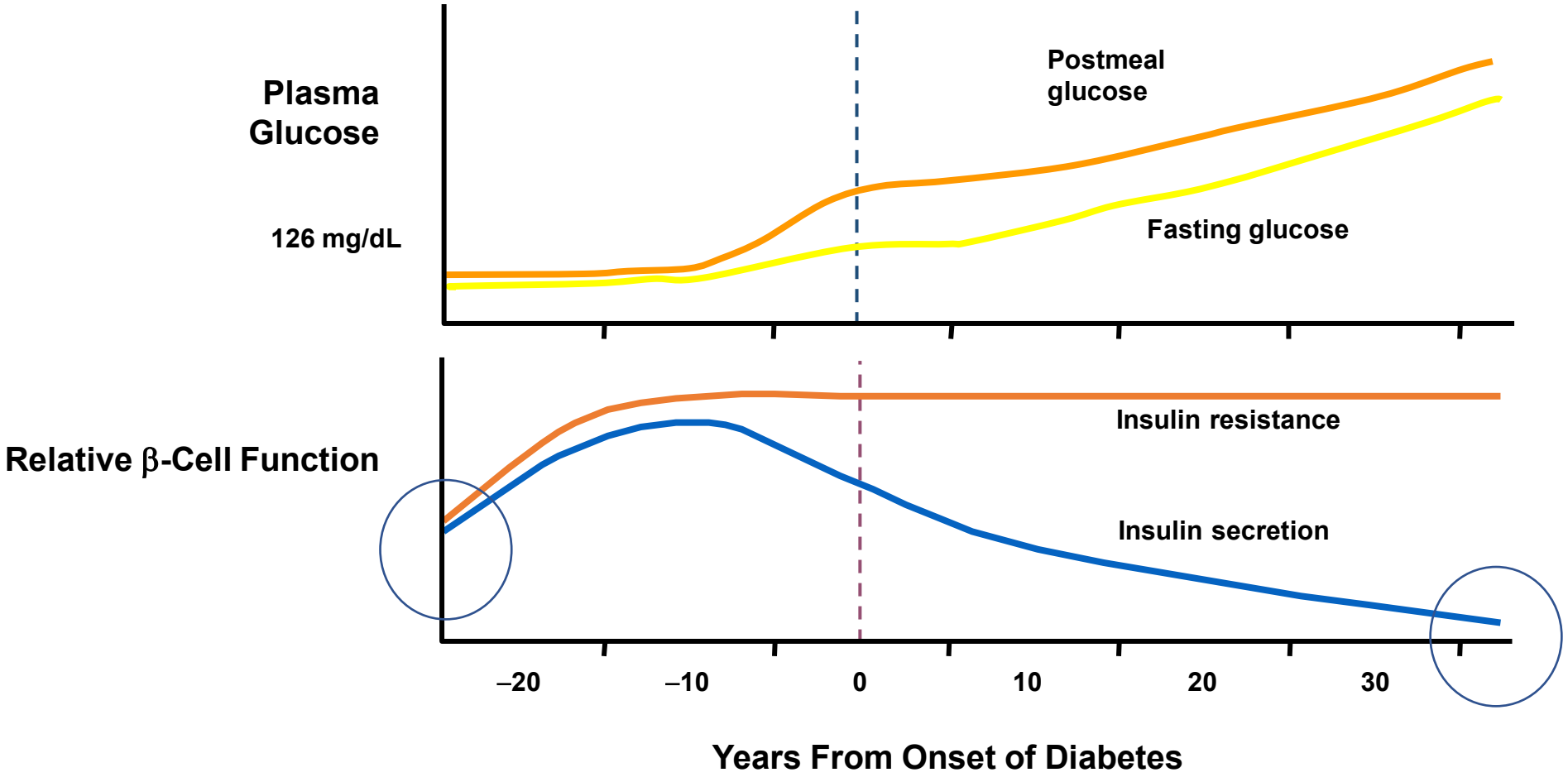
- Scientifically very difficult
- Insulin levels from a conventional glucose tolerance test require complex calculations
- A fasting insulin level with a fasting glucose level (blood tests) can be entered into a formula: HOMA-IR fasting glucose (mg/dL) × fasting insulin (µmol/L)/405.
  - HOMA-IR can’t be calculated in setting of hyperglycemia
  - Levels <2 are normal insulin sensitivity
  - Levels 2-3 are mild insulin resistance
  - Level over 3 are more significant insulin resistance

# What is the difference between insulin resistance and diabetes or pre-diabetes?

- In insulin resistance, high levels of insulin are needed to maintain normal glucose levels
- In pre-diabetes and type 2 diabetes, glucose levels rise despite the presence of insulin
- In most patients with type 2 diabetes or pre-diabetes, insulin resistance is present



# Natural History of Type 2 Diabetes

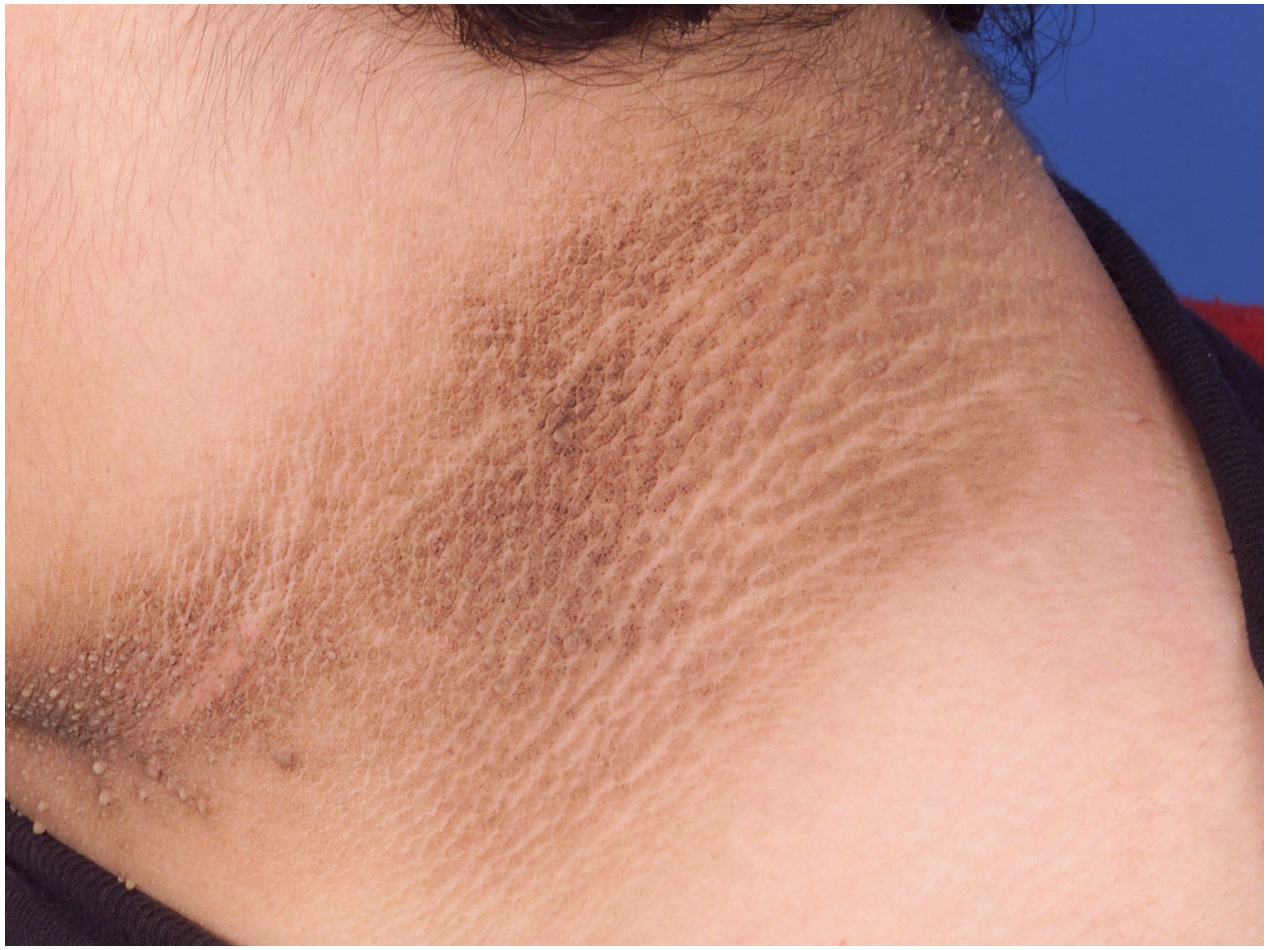





Adapted from: Bergenstal R and Kendall D. International Diabetes Center (IDC) Minneapolis, Minnesota.

# Signs of insulin resistance on physical exam

- Acanthosis Nigricans (dark velvety skin behind the neck or under the arms)
- Skin Tags
- Increased Abdominal Circumference

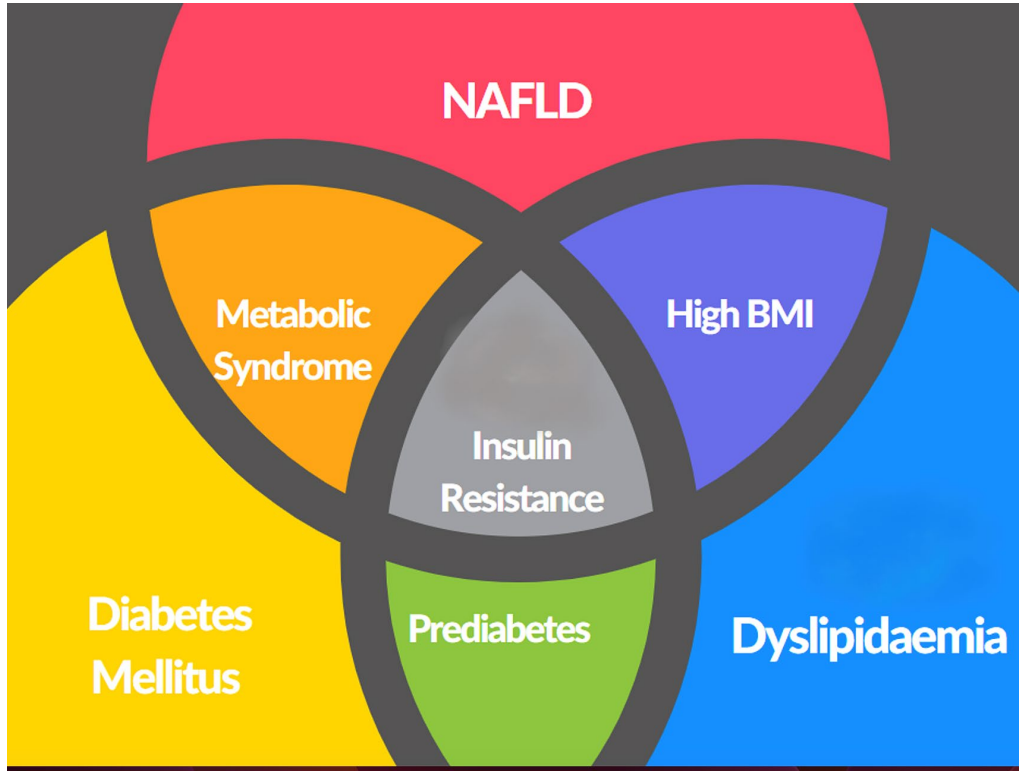




https://coem.com/blog/acanthosis-nigricans/

# Conditions that often present with insulin resistance

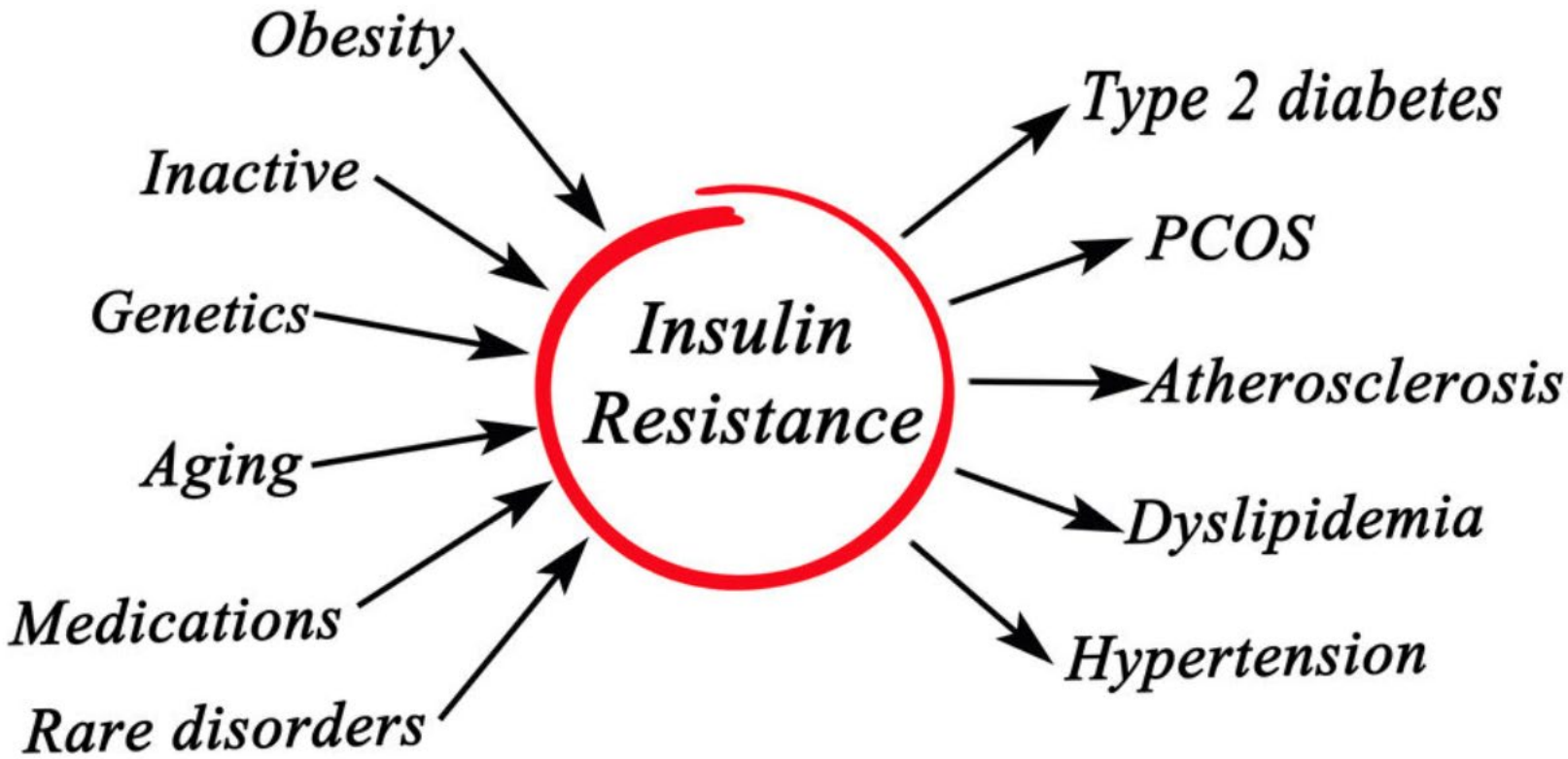
- Polycystic Ovarian Syndrome (PCOS)
- Non-alcoholic Fatty Liver Disease

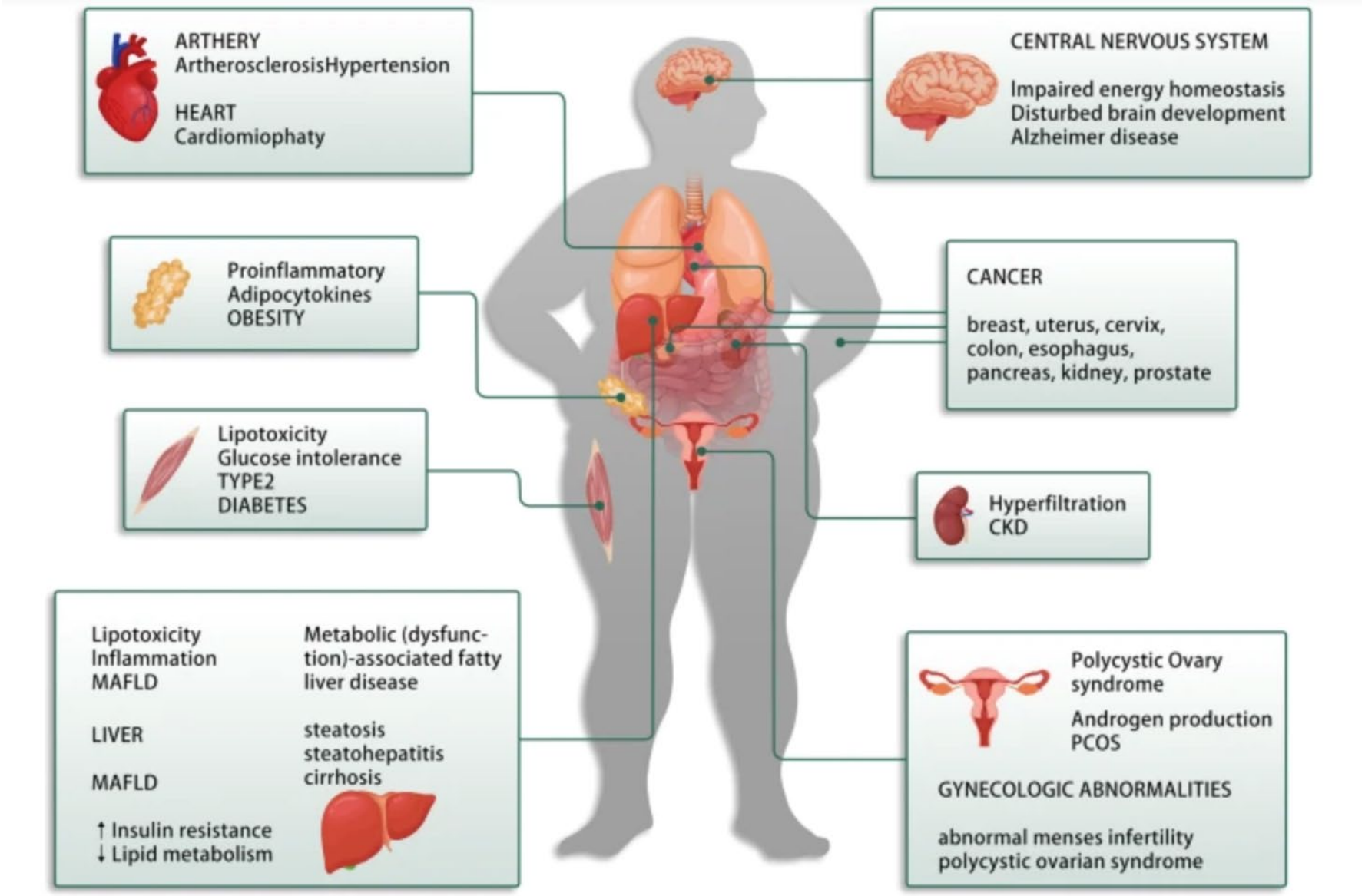





Cureus 14(4): e23806. doi:10.7759/cureus.23806

# Causes and Consequences of Insulin Resistance






Insulin resistance related diseases in human

Signal Transduction and Targeted Therapy (2022)7:216

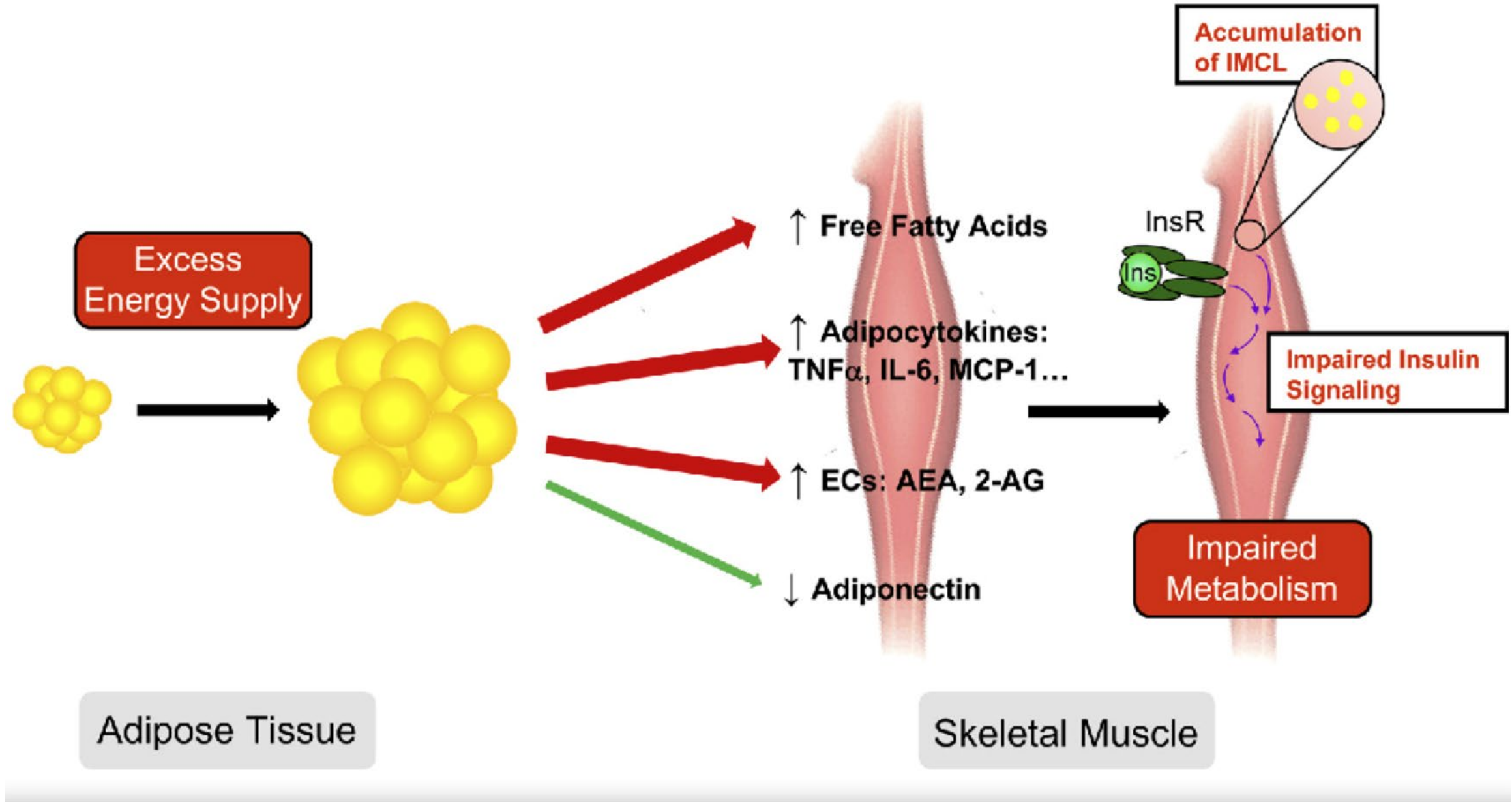
# Part 2: Looking at Causes of Insulin Resistance

- Obesity
- Hepatic disorders
- Glucocorticoid excess

# Obesity and Insulin Action

- Elevated free fatty acids from nutrient excess promote ectopic fat deposition
- Obesity expands different fat depots
  - Visceral
  - Subcutaneous
  - Hepatic/myocellular (ectopic)
- Different fat stores may differentially impact insulin action

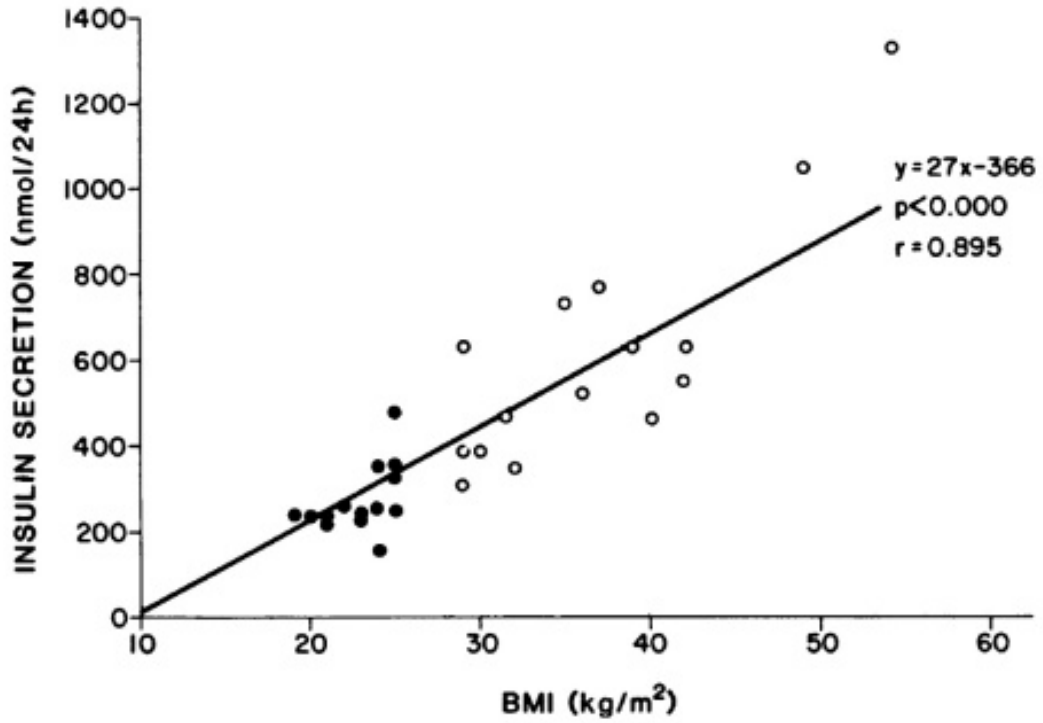
  Hepatic fat > visceral fat > subcutaneous fat






Am J Physiol Endocrinol Metab 2009 Nov;297(5):E1004-12

# Increase in insulin secretion with higher BMI




Because insulin resistance increases with increase in fat stores, more insulin is needed to maintain glucose levels

# Ethnic Differences and Insulin Resistance

| | European | Chinese | South Asian | Native American |
|---|---|---|---|---|
| BMI | 27.5 | 23.8 | 26.1 | 31.9 |
| HOMA-IR (measure of insulin resistance) | 2.12 | 2.23 | 3.03 | **4.85** |

Large cross-sectional study of Canadians (~300 participants per ethnic group)

Glucose and insulin levels were measured in the fasting state



Diabetes Care 33:1629, 2010

# Ethnic Differences and Insulin Resistance

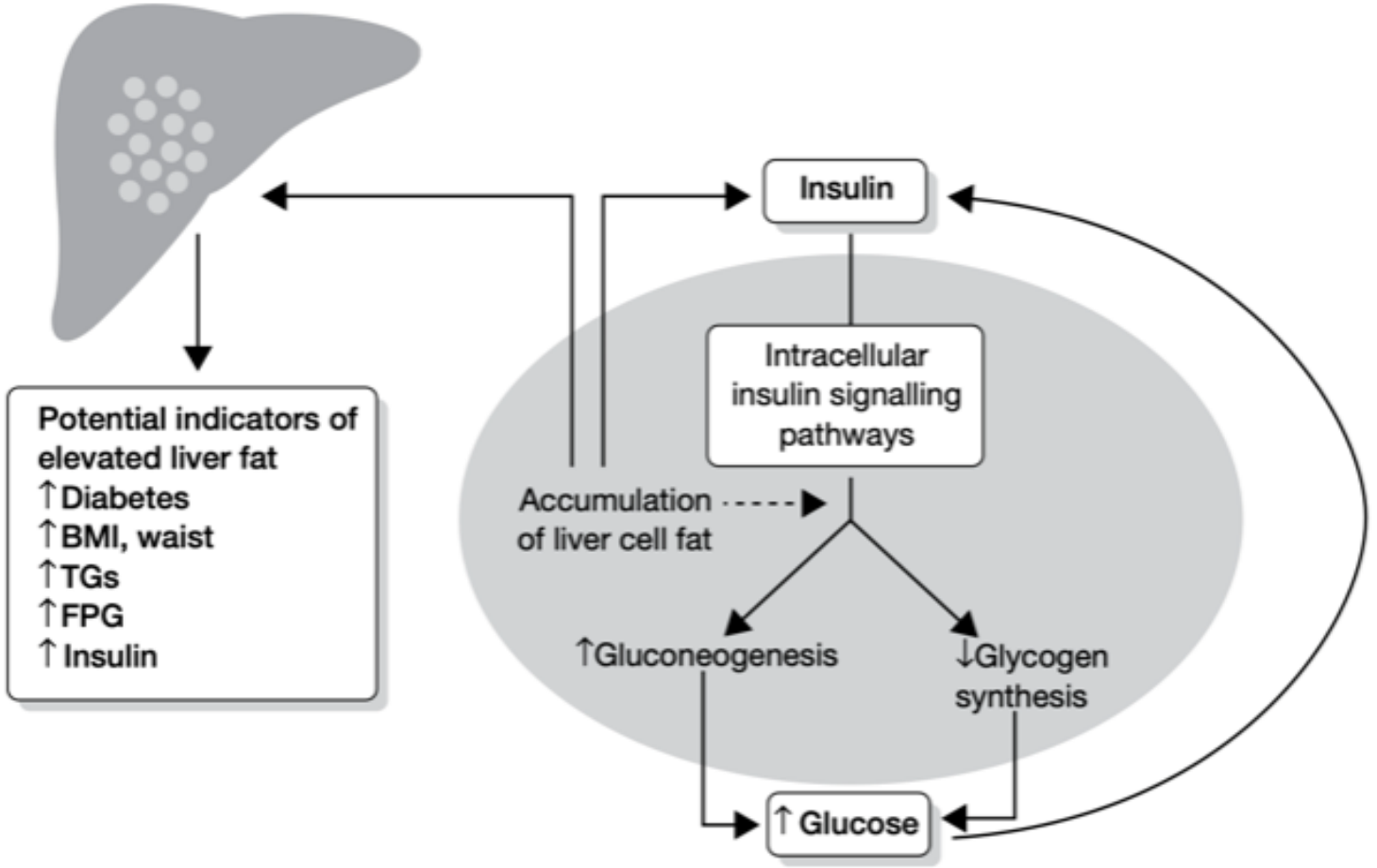
- Food frequency questionnaires were assessed for glycemic index (how much specific foods raise blood glucose level)
- In obese Native American and South Asian participants, there was a larger decrease in adiponectin levels (insulin sensitizer) for every given increase in glycemic index (vs European participants)
- No difference seen between ethnic groups in non-obese participants
- South Asian and Native American participants also had a proportionally greater increase in insulin resistance (higher HOMA-IR) for a given decrease in adiponectin



Diabetes Care 33:1629, 2010

# Fatty Liver: Cause and Consequence of Insulin Resistance

- Insulin resistance associated with fat accumulation in liver and increased circulating FFA
- Those conditions promote inflammation and endoplasmic reticulum stress
- These factors then maintain the insulin resistant state

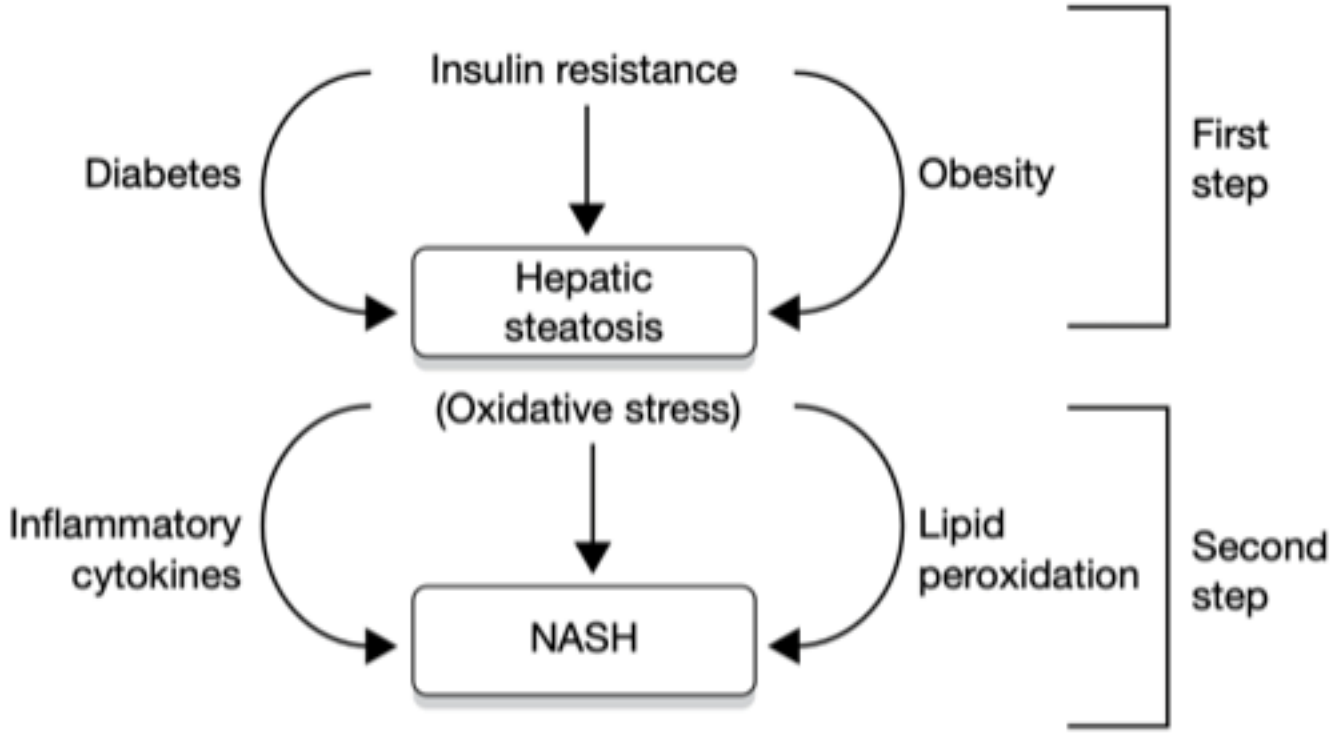





Health Technology Assessment 2011; Vol. 15: No. 38 ISSN 1366-5278

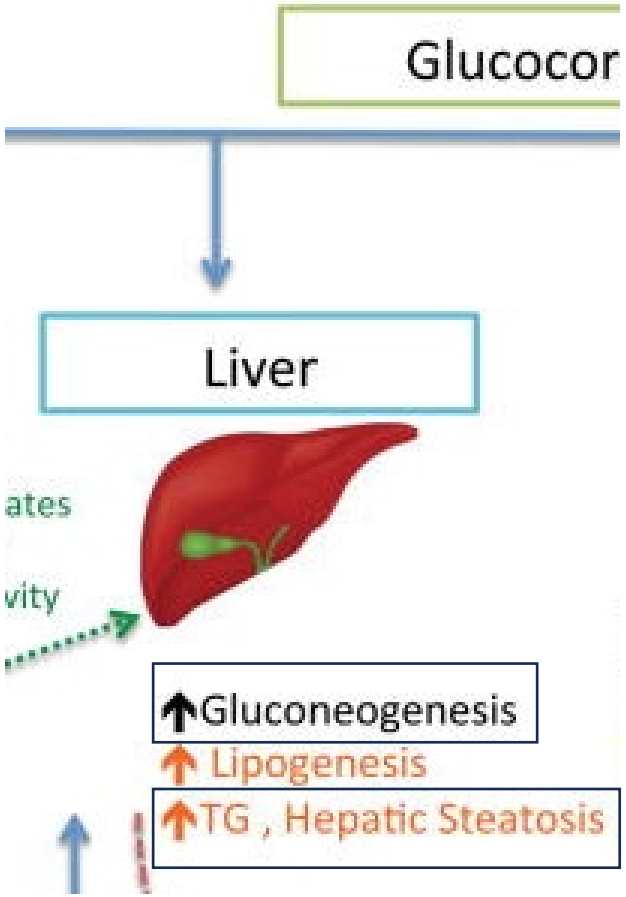
# Fatty Liver: Cause and Consequence of Insulin Resistance

- Inflammation and endoplasmic reticulum stress can cause NAFLD to progress to NASH (which is the progressive form of NAFLD that can lead to cirrhosis)




AJ McCullough. J Clin Gastroenterol 2006;40(Suppl. 1):17-29

# Glucocorticoids and Insulin Resistance:




JCI 122:3854, 2012



Endocrinol Metab Clin North Am. 2014 Mar; 43(1): 75–102. doi: 10.1016/j.ecl.2013.10.005

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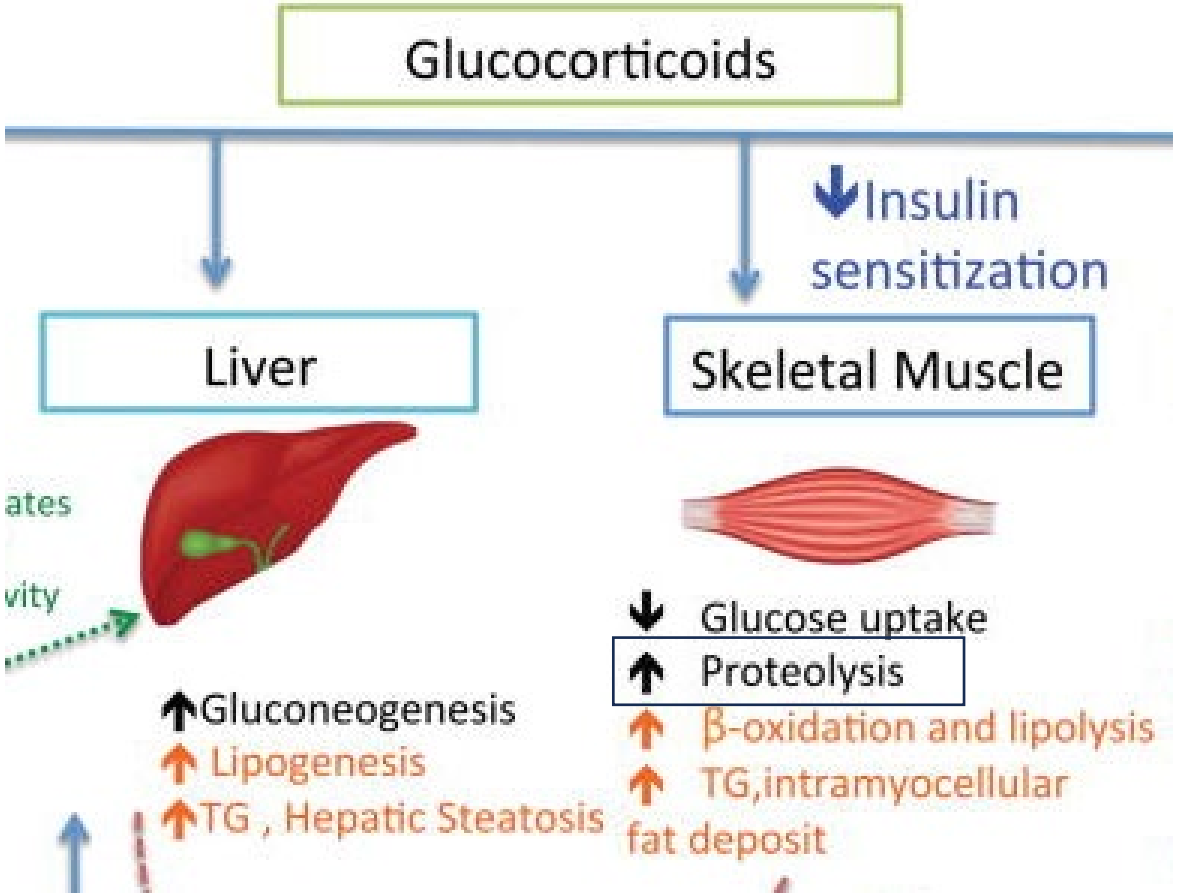


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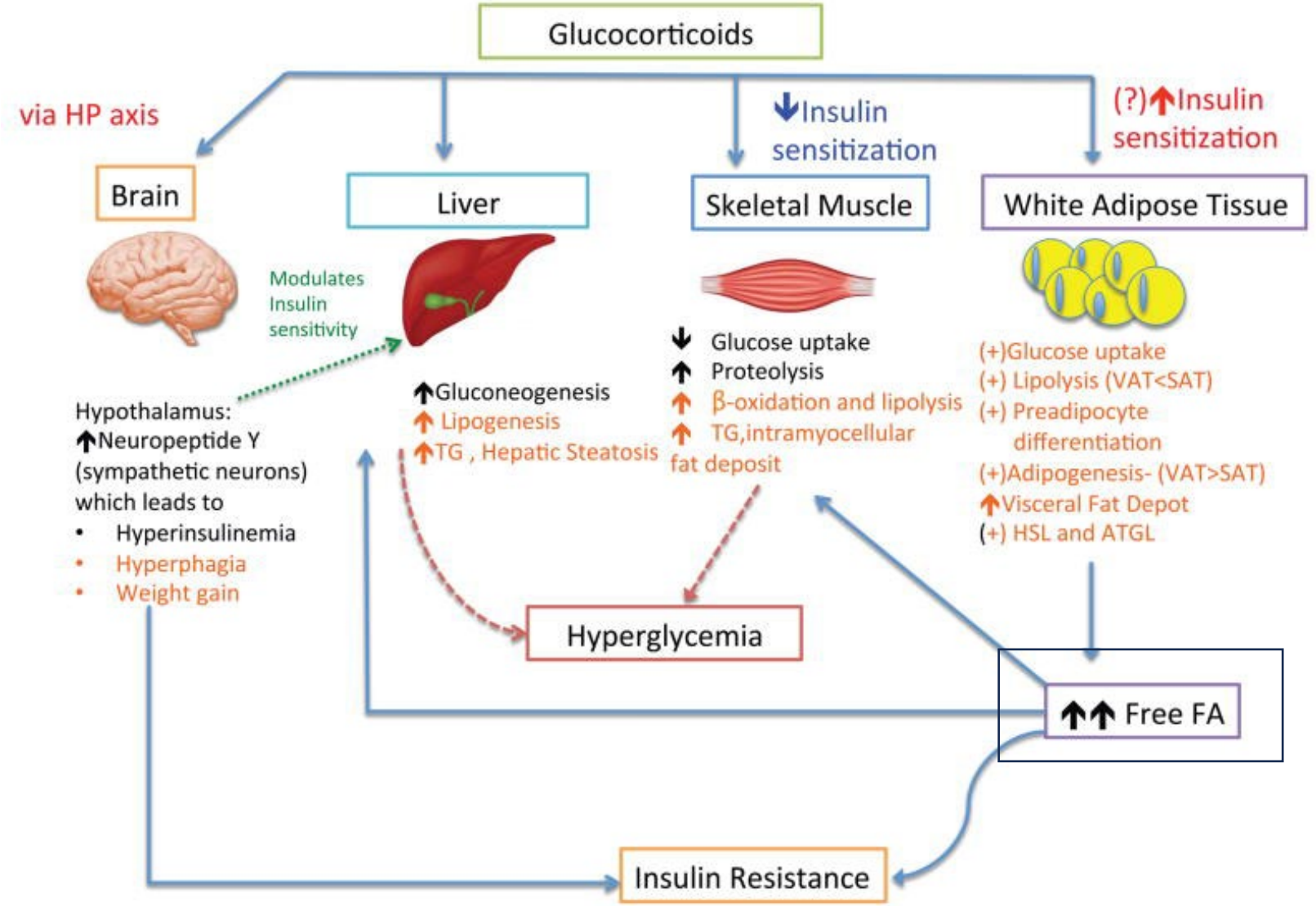


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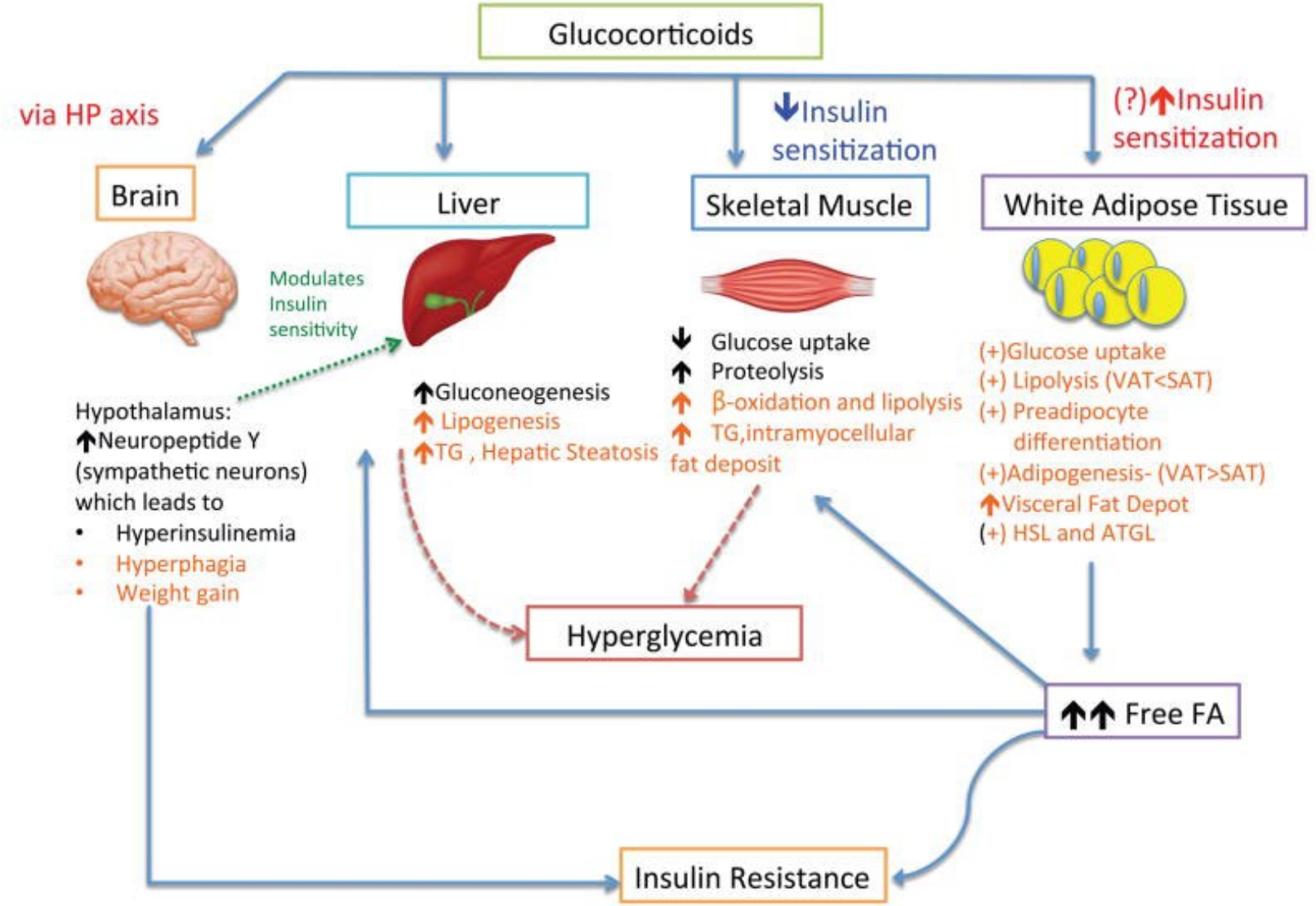



JCI 122:3854, 2012

Endocrinol Metab Clin North Am. 2014 Mar; 43(1): 75–102. doi: 10.1016/j.ecl.2013.10.005

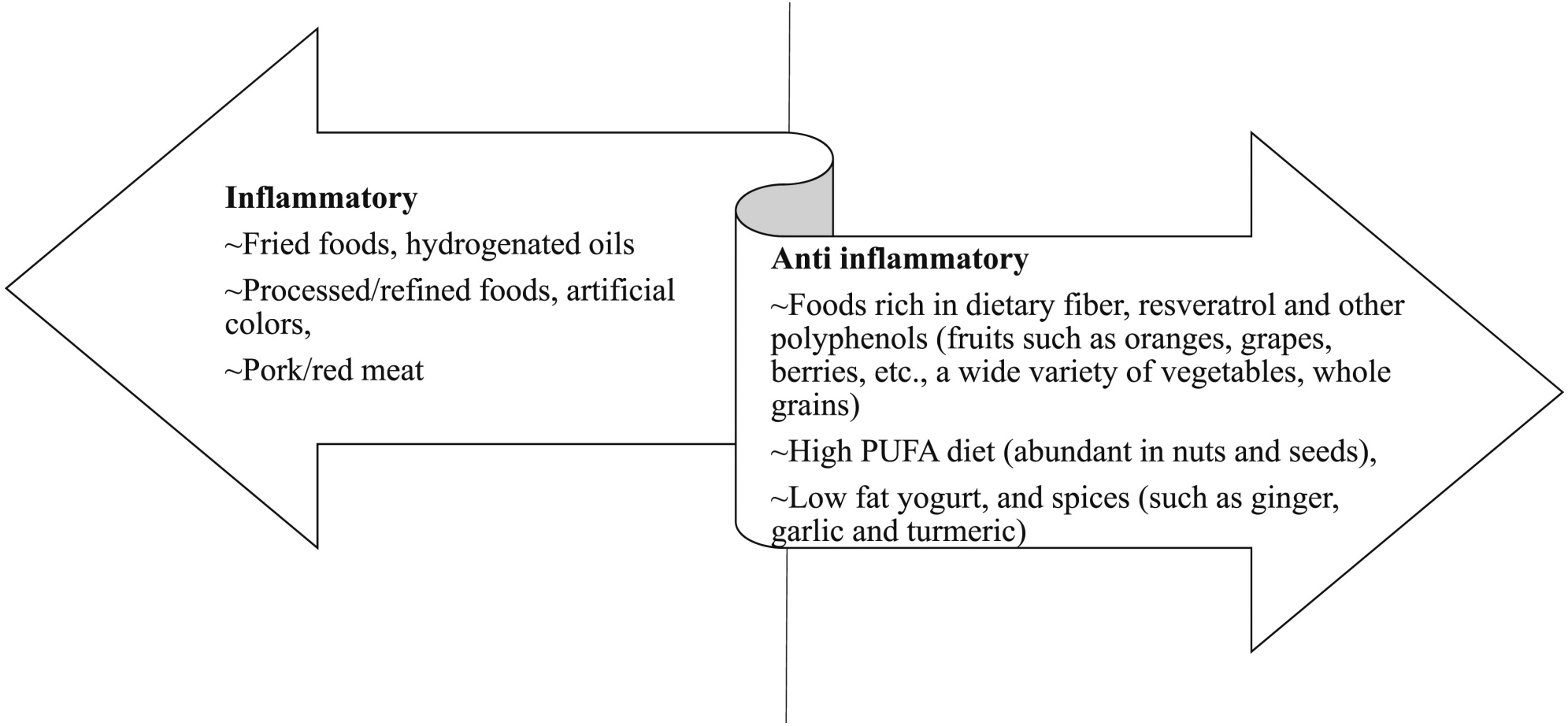
# Part 3: Strategies to Improve Insulin Resistance

- Nutrition
- Physical Activity
- Pharmacologic Agents
- Weight Loss




https://www.tcimedicine.com/post/natural-ways-to-improve-blood-sugar-and-insulin-sensitivity

# Nutrition, inflammation and insulin resistance



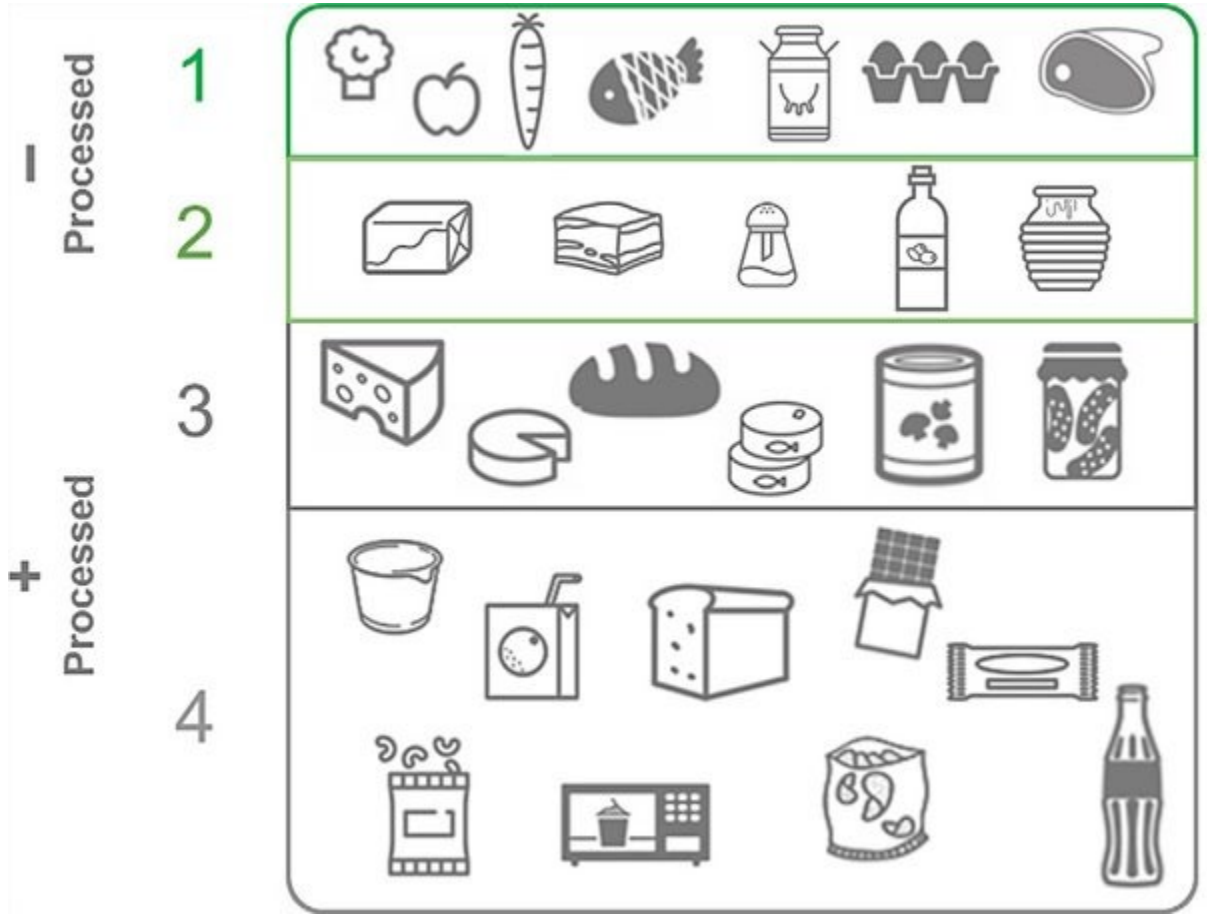



*J Clin Endocrinol Metab*, Volume 104, Issue 12, December 2019, Pages 6118–6128

# Nutrition in Type 2 Diabetes

- Mediterranean, low-calorie, low-fat eating plan
- Unclear whether a low-carbohydrate eating plan is beneficial for pre-diabetes
- Overall **quality of food is important** (as measured by the Alternative Healthy Eating Index)
  - emphasis on whole grains, legumes, nuts, fruits and vegetables, and minimal refined and processed foods
- Higher intakes of nuts, berries, yogurt, coffee, and tea are associated with reduced diabetes risk
- Sugar-sweetened beverages are associated with an increased risk of type 2 diabetes

# NOVA diet classification system




**Raw and minimally processed foods**

**Processed culinary ingredients**

**Processed foods**

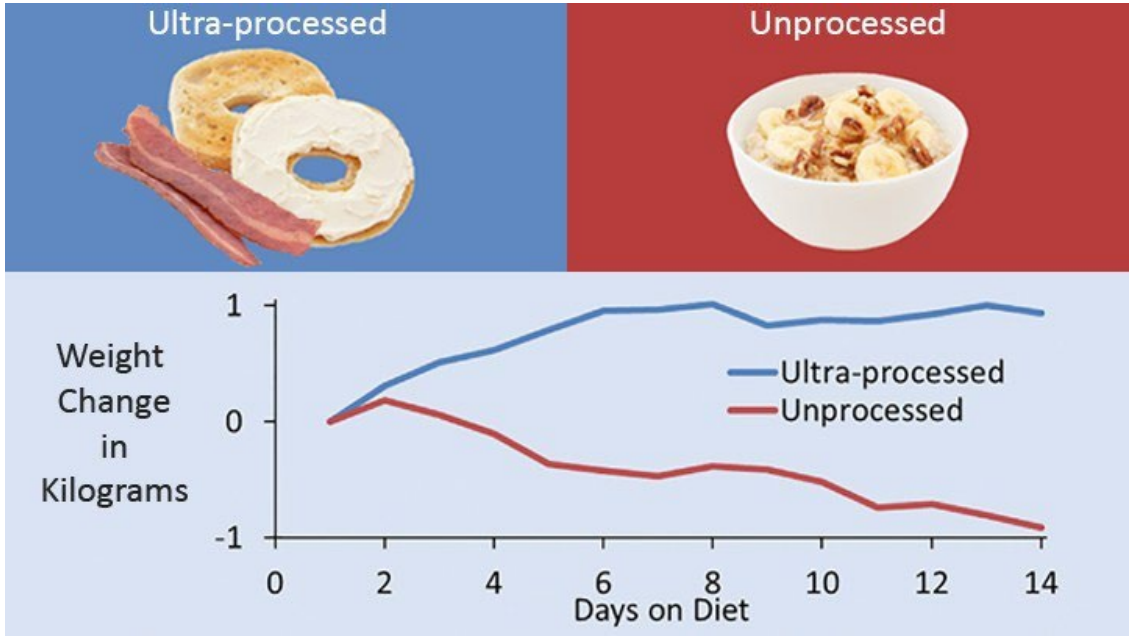
**Ultraprocessed foods and drinks**



Monteiro CA, Cannon G, Levy RB et al. NOVA. The star shines bright. World Nutrition 2016, 7, 1-3, 28-38

# Weight gain and ultra-processed foods

- Researchers at the NIH investigated whether people ate more calories when exposed to a diet composed of ultra-processed foods compared with unprocessed foods
- Despite the diets being matched for daily presented calories, sugar, fat, fiber, and macronutrients, people consumed more calories when exposed to the ultra-processed diet as compared to the unprocessed diet
- People gained weight on the ultra-processed diet and lost weight on the unprocessed diet






Hall KD et al. Cell Metab. 2019 May 16

# Keep it simple.

Eat food.
Not *too* much.
Mostly plants.

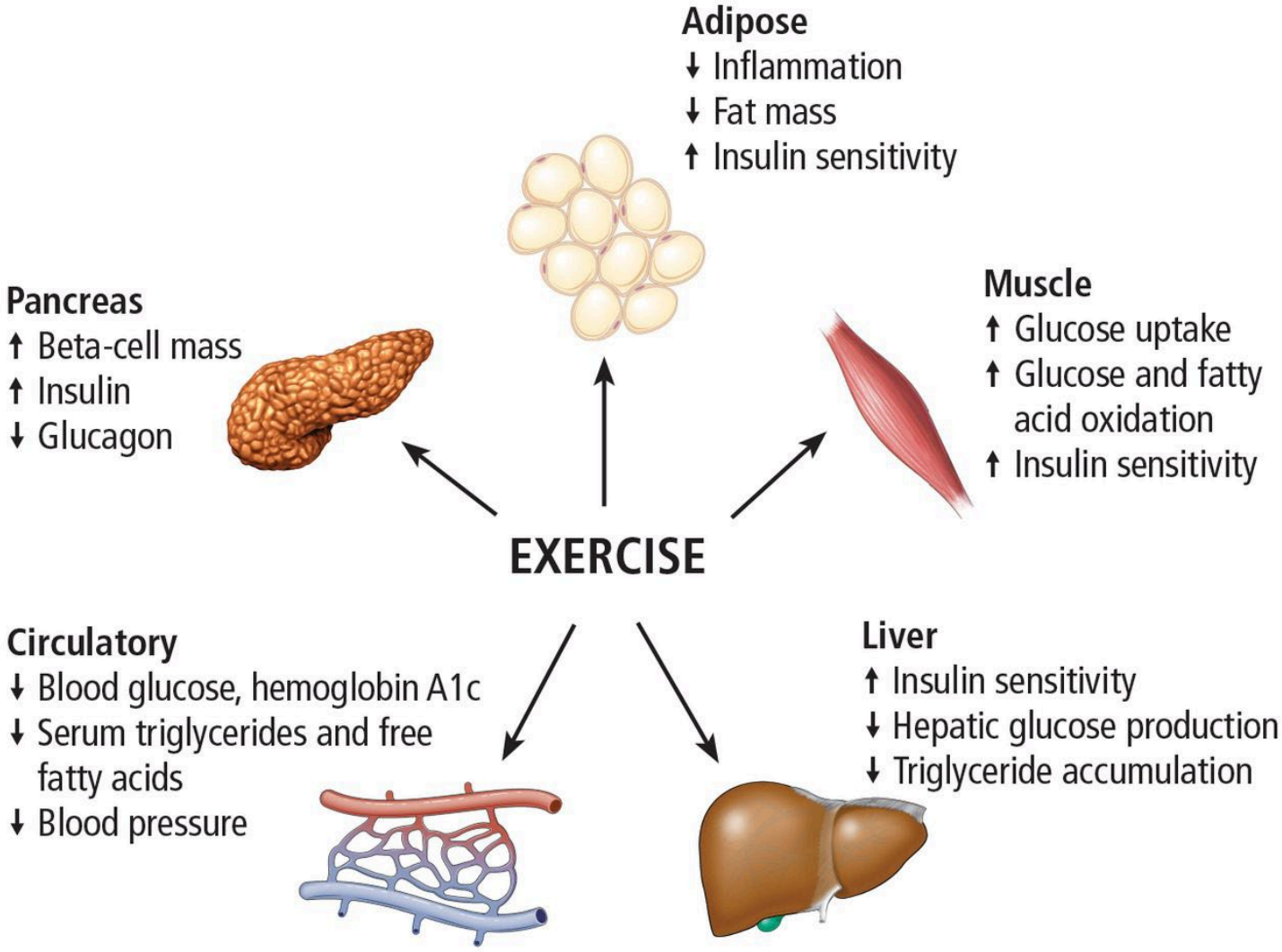
Michael Pollan,
In Defense of Food

# Exercise

- Both immediate and longer-term effects on insulin resistance
- Immediate effect of a single exercise bout can be seen for up to 72 hours post-exercise
  - Single bout of moderate intensity exercise (45 min) could improve glucose uptake by up to 40% (Perseghin et al, NEJM, 1996)
- If repeated regularly, long-term chronic improvement to insulin sensitivity (IS)
- Many studies show a dose response relationship
- Muscle contraction resulted in GLUT4 translocation into cell membrane, increasing glucose uptake

Bird SR, Hawley JA. BMJ Open Sport Exerc Med. 2016; 2(1): e000143. doi: 10.1136/bmjsem-2016-000143
Venkatasamy VV, Pericherla S, Manthuruthil S, Mishra S, Hanno R. J Clin Diagn Res. 2013 Aug;7(8):1764-6. doi: 10.7860/JCDR/2013/6518.3306..

# Exercise




Kirwan, JP, Sacks J, Nieuwoudt, S. Cleveland Clinic Journal of Medicine July 2017, 84 (7 suppl 1) S15-S21; DOI: https://doi.org/10.3949/ccjm.84.s1.03

# Pharmacologic Options

- Metformin
- Thiazolidinediones
- GLP-1 receptor agonists
- Concentrated forms of insulin

# Metformin

- Has been the foundation of T2DM pharmacotherapy. Also can be considered in pre-diabetes
- Complex mechanisms of action, but is an “insulin sensitizer”
  - Major effect is to decrease hepatic glucose output by inhibiting gluconeogenesis

| eGFR | Initiation | Continuation |
|---|---|---|
| >45 | OK to initiate | Max dose 2550 mg total daily |
| 30-45 | Not recommended | - FDA: If already on metformin and eGFR falls to between 30-45, assess risks/benefits of continuing<br>- In practice: Consider lowering the dose to maximum of 1000 mg total daily |
| <30 | Contraindicated | Discontinue |

# Use of metformin lowers insulin dose

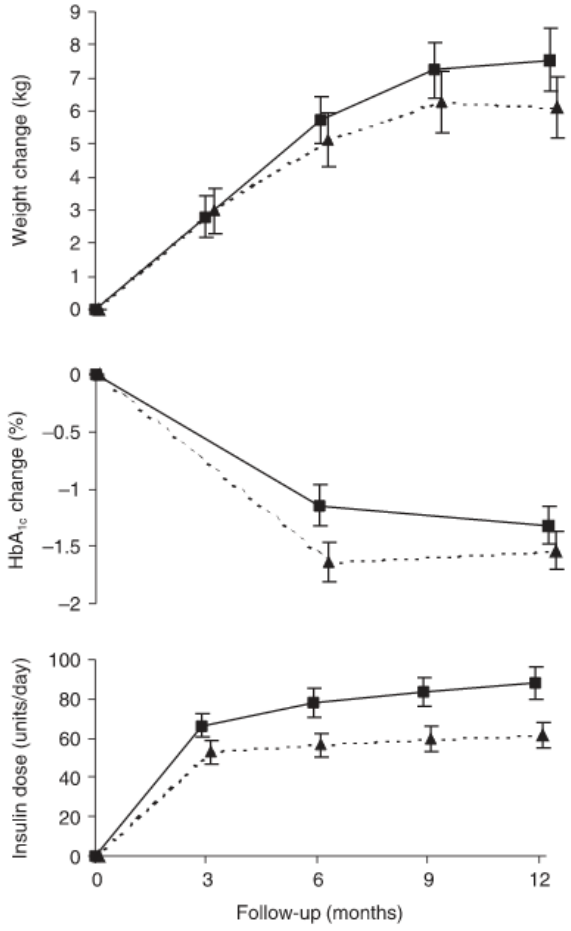



**Figure 2** Change in mean weight (upper panel), $HbA_{1c}$ (middle panel) and total insulin dose (lower panel) over the duration of the trial for each treatment group (▲, metformin, ■, placebo). 95% confidence intervals are shown.

- Type 2 patients with poor control on oral agents
- Patients randomized to insulin alone or insulin with metformin
- After 1 year, insulin dose was lower (25 units/day) and weight gain less (1.5 kg) in metformin-treated patients

Diabetic Medicine 22:634,2005

# Thiazolidinediones: Improve Insulin Sensitivity but at a cost

- Available since 1997
- Pioglitazone (preferred) and rosiglitazone (not recommended)
- Mechanism:  PPAR-γ activation, increased peripheral glucose uptake, decrease lipolysis.
- Dosing: daily, takes weeks-months for full effect, max effective dose = max dose.
- A1c lowering:  1-2%
- Pros:  efficacy, metabolic effects, daily dosing, no hypoglycemia, ?preservation of beta-cell function.
- Cons: weight gain, edema/CHF, CV controversy, fractures, urologic cancers?

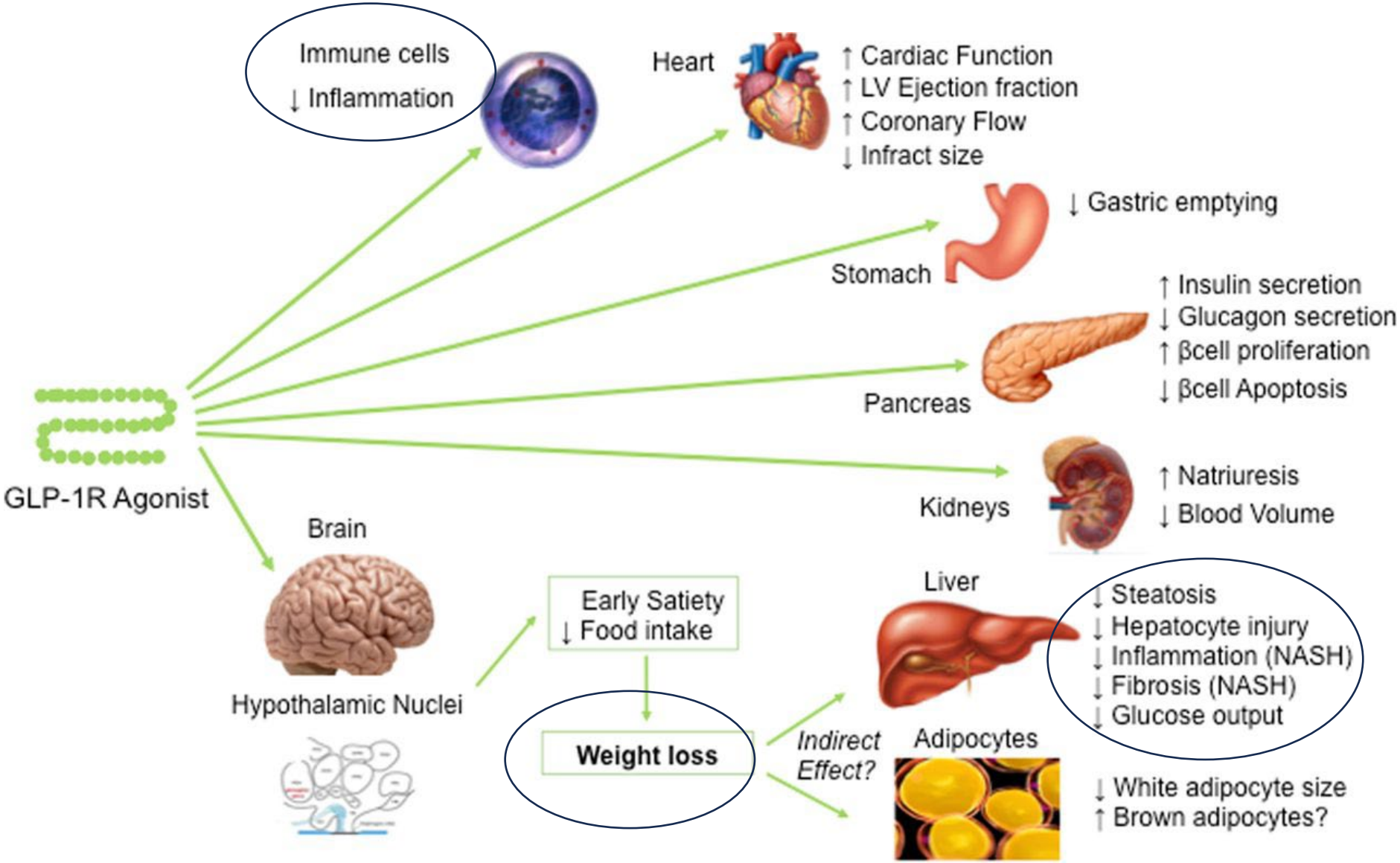
# GLP-1 receptor agonists

- Medications that are approved for use in type 2 diabetes
- Mimic the incretin hormone GLP-1 (gut hormone)
- Many effects including increased insulin release, decreased gastric emptying, decreased appetite, and often, weight loss
- Examples include:
  - Dulaglutide (Trulicity) - once weekly
  - Semaglutide (Ozempic) – once weekly
  - Tirzepatide (Mounjaro)* – once weekly
    - *Also a GIP agonist (dual agonist)




https://www.medpagetoday.com/special-reports/features/102773

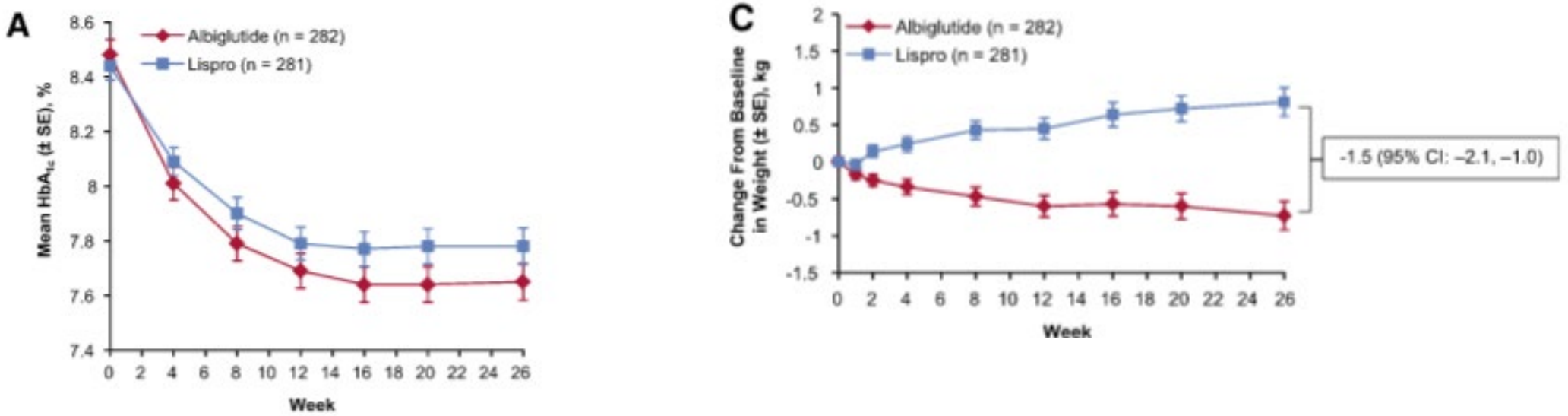
# Glucagon-like peptide-1 receptor agonists (GLP-1RAs) – Many Effects!






Gauri Dhir, and Kenneth Cusi J Investig Med 2018;66:7-10

# Combining Insulin with GLP-1 Receptor Agonists




-Trial in almost 600 patients with type 2 diabetes randomized to either weekly GLP-1 R agonist therapy or three times per day lispro as add-on to glargine
-Baseline: Mean A1C 8.5% Mean weight 95 kg Mean glargine dose 50 units



Diabetes Care 37:2317, 2014

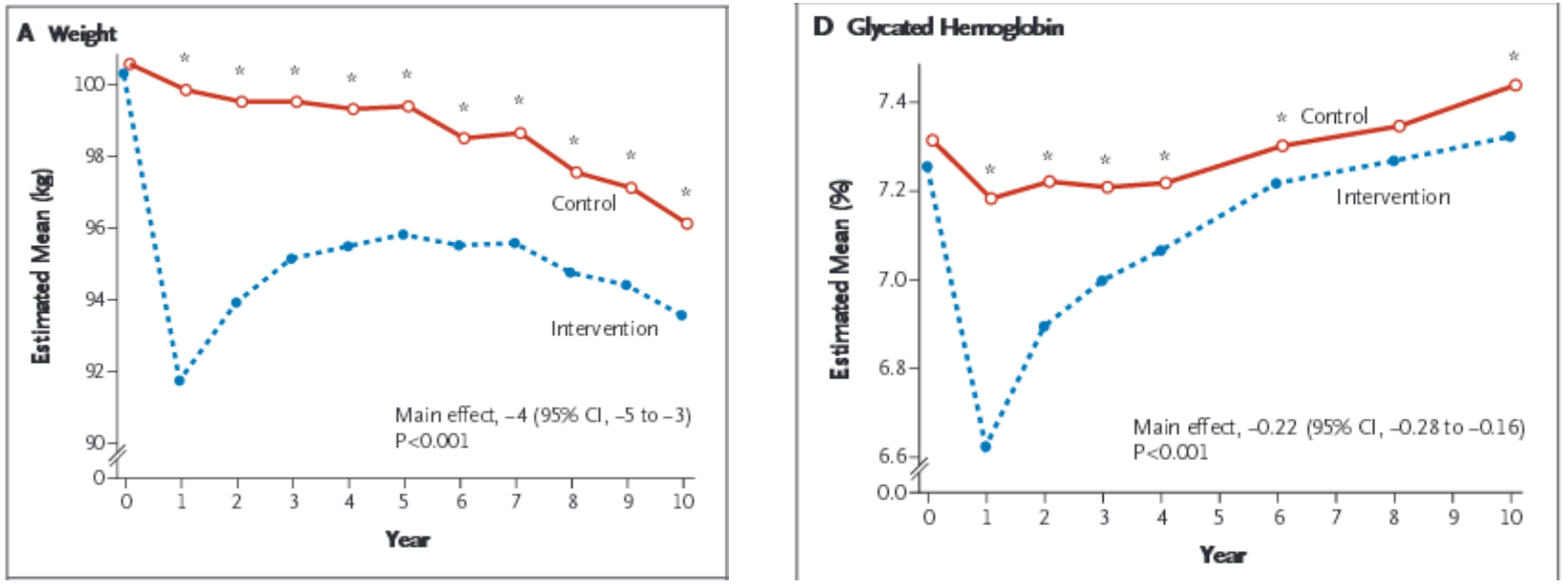
# Treatment Approaches to Insulin Resistance/High Insulin Doses

- Common definition of “high insulin requirements”: >200 units/day (also sometimes use more than 1 unit/kg/day total daily dose)
- Most important part of the assessment: **adherence**
- Try to determine if patient is taking medications and particularly insulin as prescribed
  - Query pharmacy for refills
  - Ask how they take insulin (doses over 80 units requires 2 injections if using a typical U100 pen)
- Try to determine barriers to adherence such as perception of excessive number of injections

# Give More Insulin…

- U-500 insulin is Regular human insulin
- It is 5 times more concentrated than usual U-100 insulin
- Super-concentrating insulin delays absorption and prolongs action (similar profile to NPH insulin, lasts about 12 hours)
- Other concentrated insulin forms: U-200 lispro, U-300 glargine, U-200 degludec

# Weight Loss Improves Diabetes Control




Results of the Look AHEAD trial comparing intensive lifestyle (1200-1800 cal/day and 175 minutes of exercise/week) to group education(control) in type 2 DM

NEJM 369:145, 2013

# Impact of Bariatric Surgery on Insulin Use

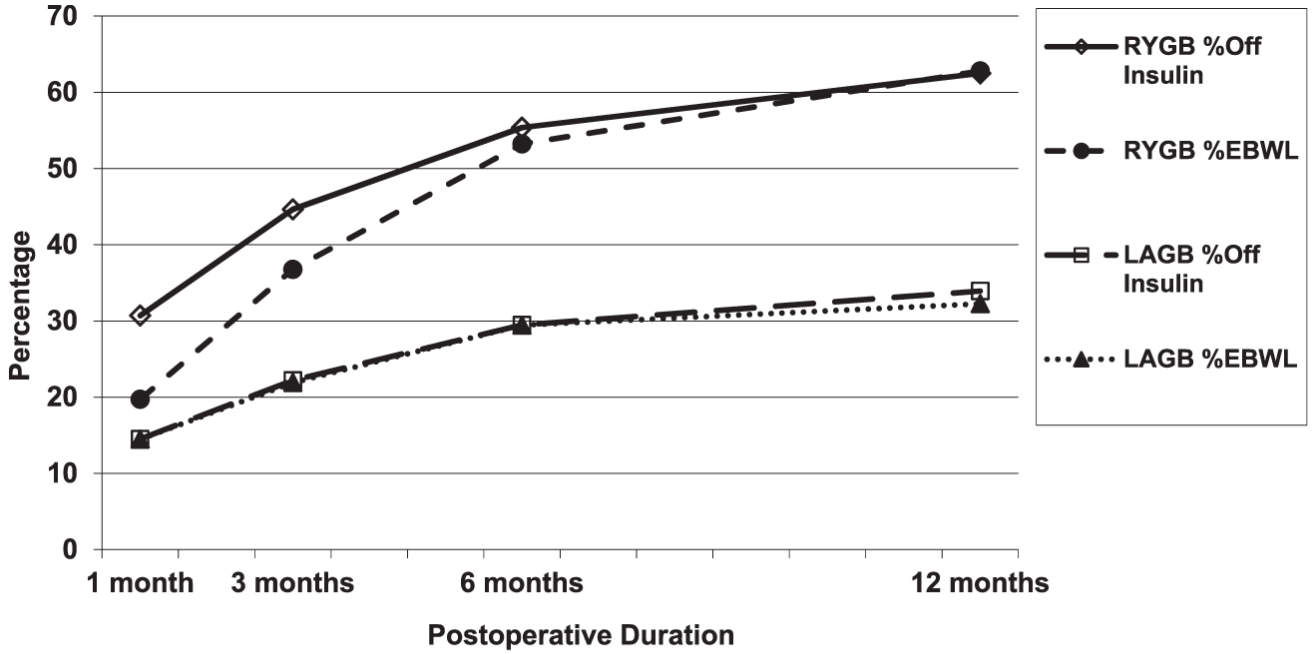
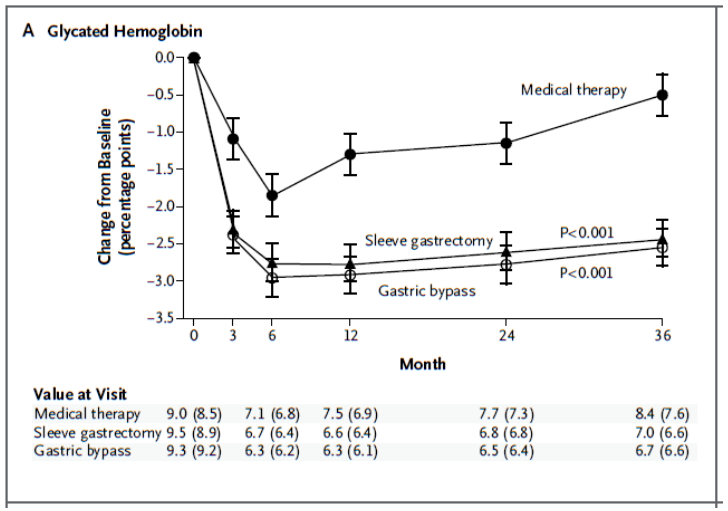


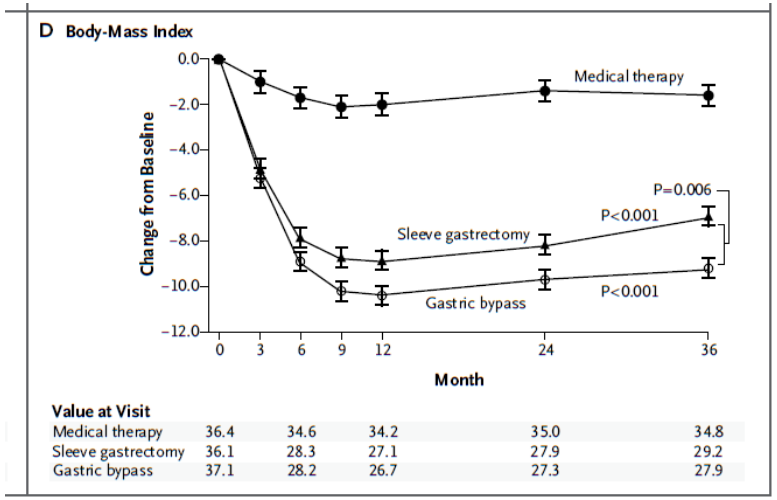

**Figure 1**—Comparison of %EBWL and percentage of patients off insulin following bariatric procedures in the overall BOLD cohort. $P < 0.001$ for all comparisons between RYGB and LAGB.

Large cohort of type 2 patients on insulin undergoing Gastric Bypass or Gastric Banding
Higher percent off insulin with RYGB. Also drop in insulin use precedes weight loss in RYGB compared to LGB

Diabetes Care 38:659, 2015

# Surgery for T2DM: 3 year data




| Intervention Group | % on insulin at start | % on insulin at 3 years |
|---|---|---|
| Medical | 52 | 55 |
| Gastric Bypass | 46 | 6 |
| Sleeve Gastrectomy | 45 | 8 |

Schauer PR *NEJM 370:2002,* 2014

# Strategies in the patient with high insulin needs

- Assess adherence and barriers to management
- Improve insulin sensitivity if possible
  - Use metformin
  - Encourage physical activity, healthy diet, and weight loss
- Add medication to insulin to help with weight loss (and insulin action)
  - GLP-1 Receptor agonists
- Make taking the insulin easier
  - U-500
- Refer for bariatric surgery

# Back to our Patient

- She was switched to U-500 three times daily and metformin
- She was screened for genetic markers of lipodystrophy: negative
- A1C improved to 6.7% for a short time
- She did not get pregnant and A1C increased to 7.4%
- She underwent gastric bypass surgery
- Weight decreased to 160 lbs from 202 lbs over 10 months
- Patient on metformin alone with A1C 5.7%

# Summary of insulin resistance:

- Definition: “Lack of response of blood sugar in the face of adequate amount of insulin”
- Difficult to define scientifically (some use HOMA-IR calculation), typically present in pre-diabetes and type 2 diabetes
- Signs and clues include: acanthosis nigricans, skin tags, increased abdominal circumference; high TGs and low HDL
- Factors that impair insulin action: obesity, fatty liver disease, glucocorticoids
- Strategies to improve insulin action:
  - Dietary - non-processed foods
  - Exercise
  - Pharmacologic - metformin, GLP-1 agonists
  - Weight loss/bariatric surgery

# Genetic Influences on IR in Native Americans

- Strong Heart Family Study: large cohort (1,800 participants) consisting of thirteen tribes from three centers: Arizona, Oklahoma and North and South Dakota
- 13.5% developed diabetes over follow up period of 6.6 years
- Blood DNA was genotyped using a “Metabo-Chip”
- Identified variants at novel loci (8) and confirmed those at known candidate diabetes loci associations (26) with measures related to beta cell dysfunction/insulin resistance

Front. Genet., 12 October 2018
Sec. Applied Genetic Epidemiology
Volume 9 - 2018 | https://doi.org/10.3389/fgene.2018.00466

# Diagnosing Metabolic Syndrome

| Metabolic Syndrome | Diagnostic Criteria |
|---|---|
| 3 or more of the following criteria: | Blood pressure ≥ 130/85 mm/Hg |
| | HDL < 40 mg/dL in men<br>< 50 mg/dL in women |
| | Waist circumference > 40 in. for men<br>> 35 in. for women |
| | TG ≥150 mg/dL |
| | Fasting glucose ≥100 mg/dL |

National Cholesterol Education Program (US). Expert Panel on Detection, & Treatment of High Blood Cholesterol in Adults. (2002). *Third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III)* (No. 2). National Cholesterol Education Program, National Heart, Lung, and Blood Institute, National Institutes of Health.

# Insulin Resistance and Metabolic Syndrome

- Insulin resistance can lead to metabolic syndrome
- Most patients with metabolic syndrome have insulin resistance
- Components of metabolic syndrome should each be treated
- Metabolic syndrome can lead to increased risk for cardiovascular events

# Diabetes Epidemiology in Native Americans

| | 1975 | 2002 | P value |
|---|---|---|---|
| % diabetes | 35 | 34 | ns |
| Age at diagnosis | 40.2 | 33.6 | P<.001 |
| BMI of pts with diabetes | 30.6 | 36.3 | P< .001 |

DC 33:2383, 2010

Native Americans are being diagnosed earlier with diabetes because they are becoming more obese
Complications of diabetes directly related to duration of diabetes