CLPC Fall 2022
Diabetes update:
What's new in 2022?

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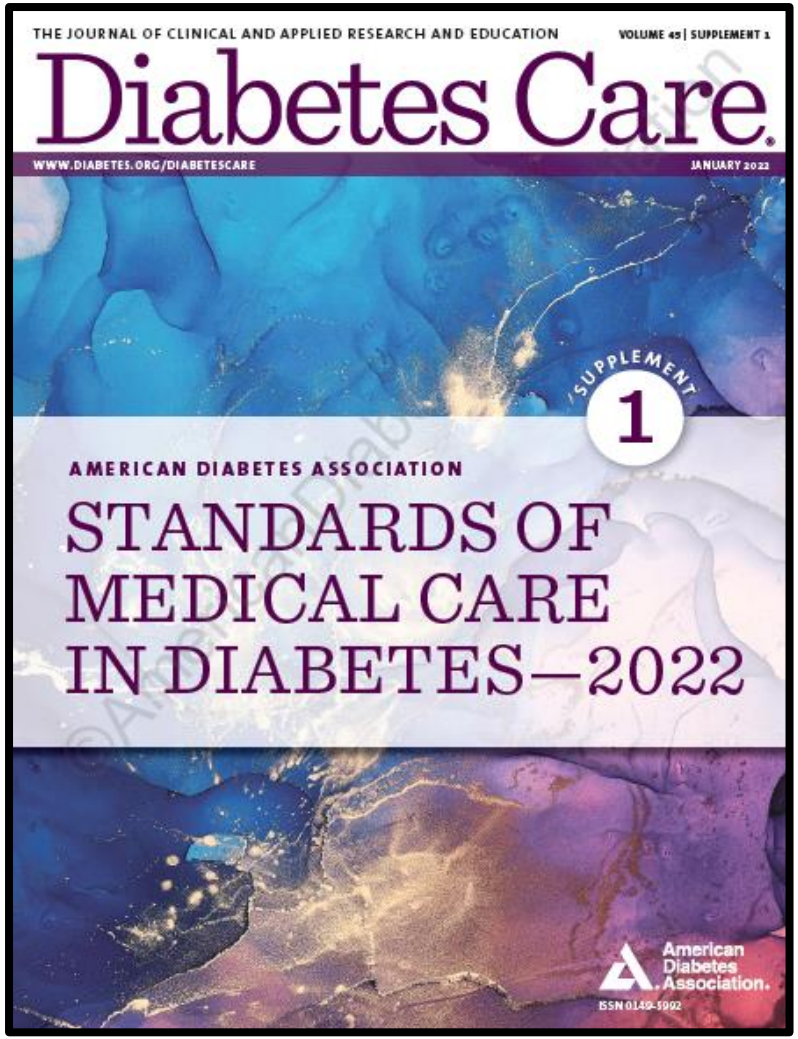
Learning Objectives

- Define/Distinguish 3 major types of Diabetes: T1DM, T2DM, and GDM (Gestational Diabetes Mellitus) and Pre-Diabetes
- Recognize appropriate lab testing for diagnosis and monitoring of Diabetes
- Describe treatment modalities for Diabetes including medications and surgery.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1
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American Diabetes Association.
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Diabetes - definition

- Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both (ADA)
- A disease in which the body's ability to produce or respond to the hormone insulin is impaired, resulting in abnormal metabolism of carbohydrates and elevated levels of glucose in the blood and urine (Oxford dictionary)

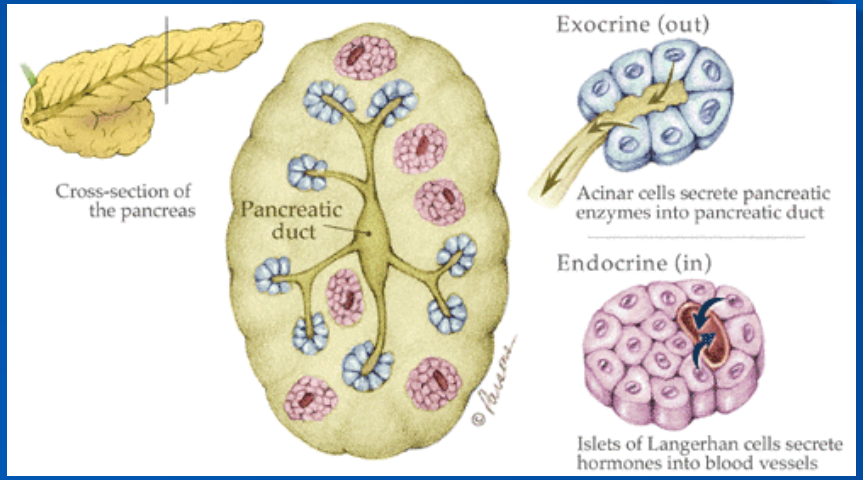
451,323
LA residents have diabetes.

That fills Tiger Stadium 4.4 times!

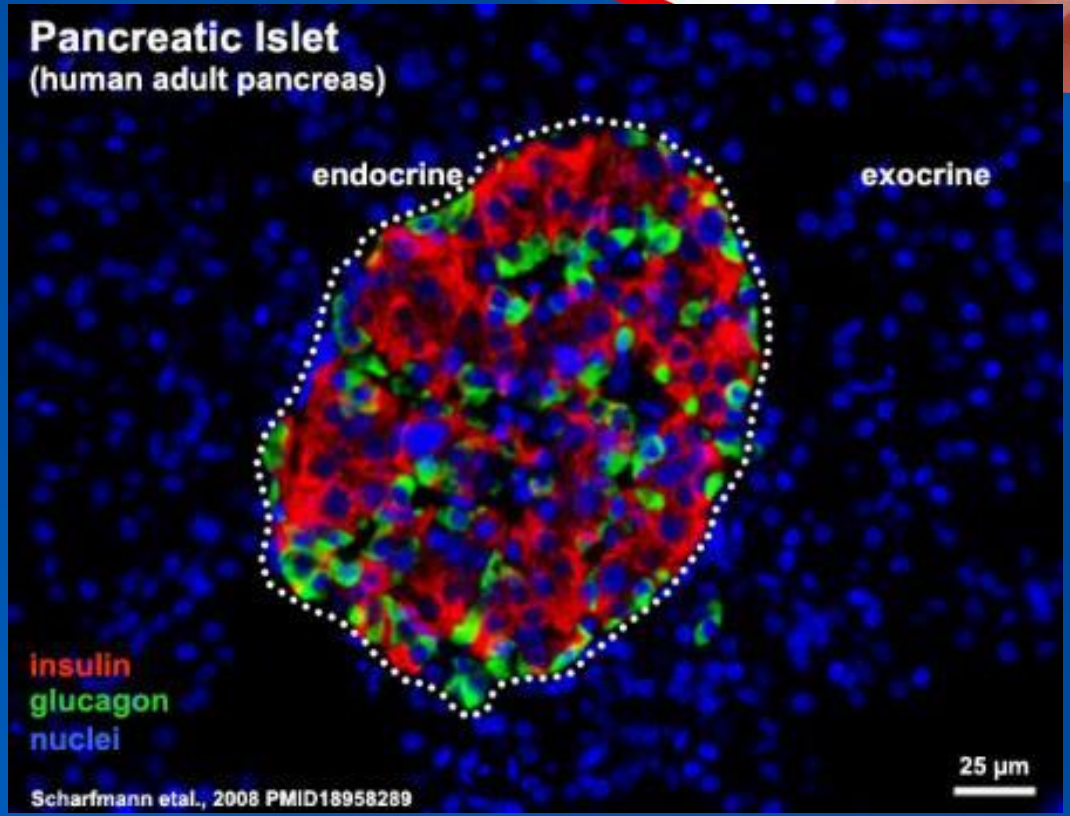
According to the American Diabetes Association, 1.27 million people in LA have prediabetes - and most don't even know it!

This fills the Superdome 16.6 times!

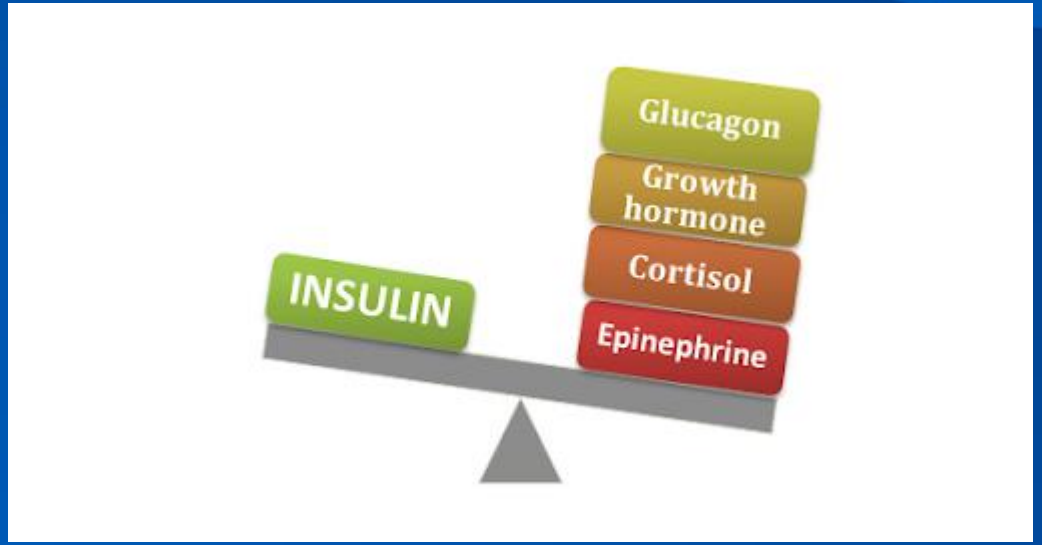
The Pancreas and metabolism



Cells of the pancreas



Insulin and counter-regulatory hormones

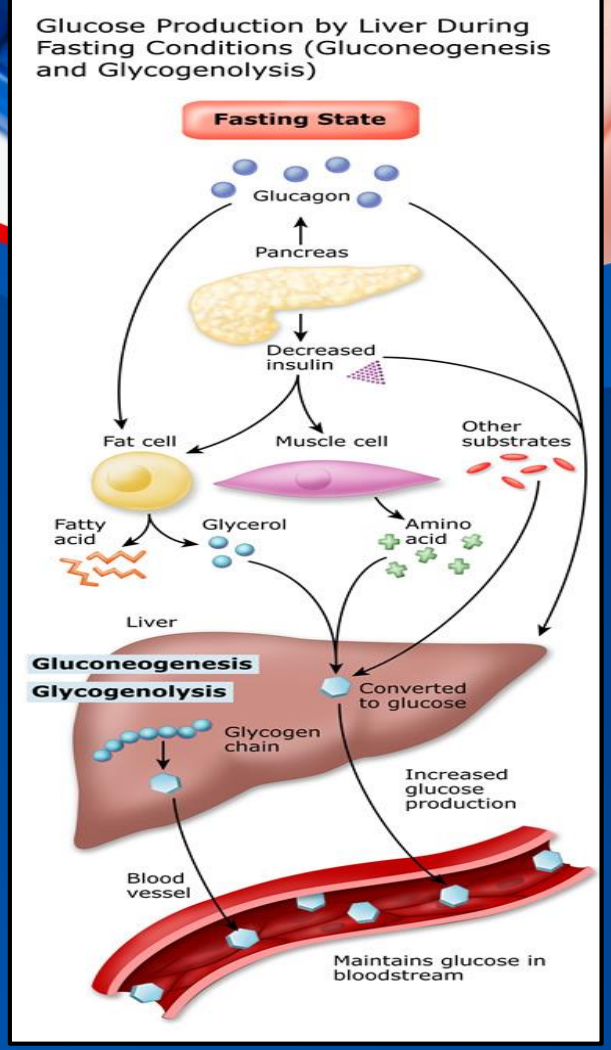


Le T, et al. (2017). *First Aid for the USMLE Step 1, 2017, A Student-to-Student Guide.* New York: McGraw Hill.

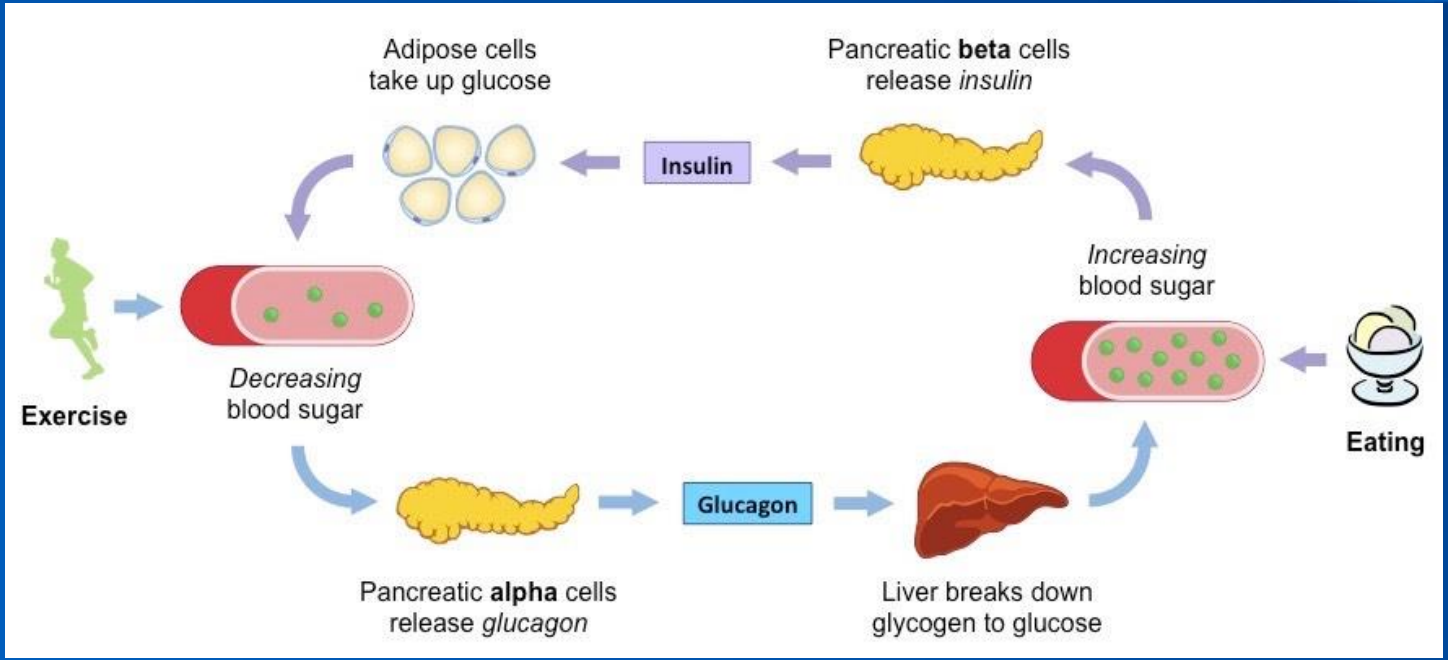
Role of the Liver:
Both stores and produces glucose:
Helps keep blood glucose constant

Gluconeogenesis

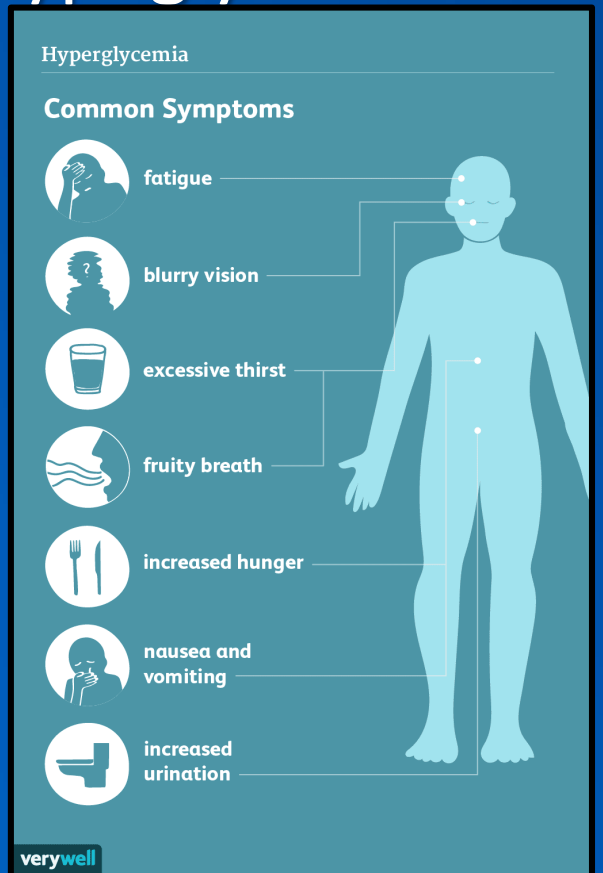
Glycogenolysis

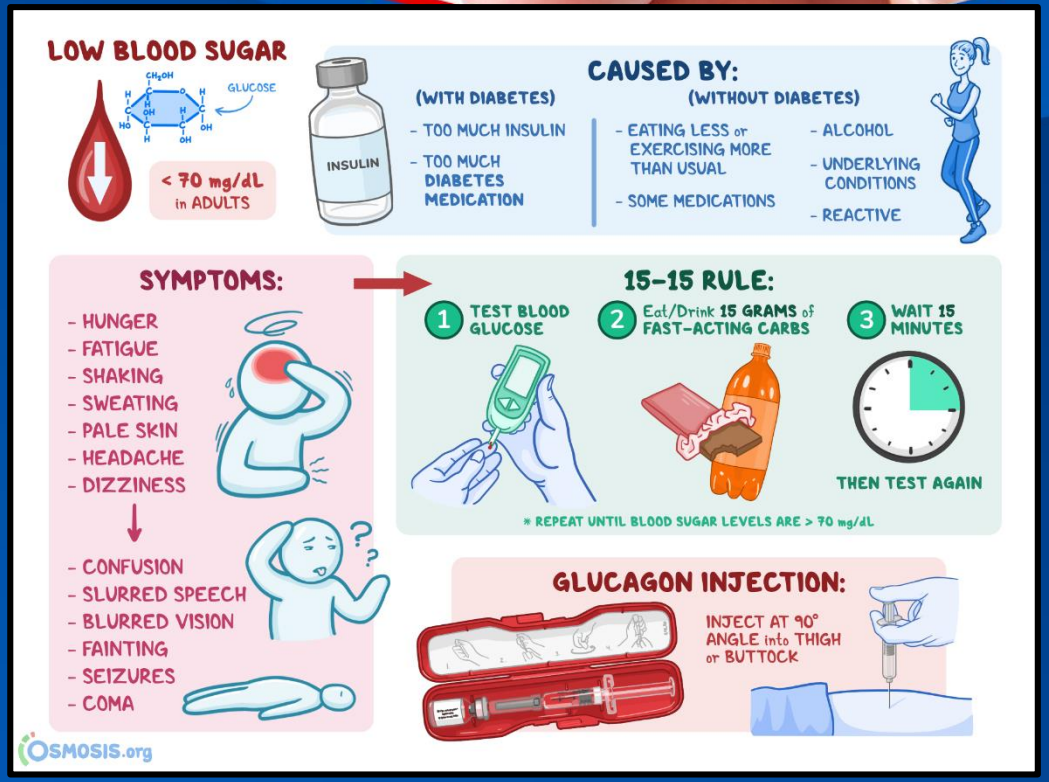


Insulin and glucagon are released by β and α cells to control blood glucose concentration



Hyperglycemia and Hypoglycemia





Summary

TABLE 1. Insulin action in various tissues

In the pancreas
• Directly inhibits glucagon release
In the liver
• Stimulates glycogen synthesis and inhibits glycogenolysis • Stimulates glycolysis and inhibits gluconeogenesis
In the muscle
• Stimulates glucose uptake and glycogen synthesis
In the adipose tissue
• Stimulates glucose uptake • Inhibits triglyceride breakdown

TABLE 2. Glucagon action in the liver

Stimulates gluconeogenesis and glucose release
Inhibits glycolysis
Inhibits fatty acid synthesis
Stimulates amino acid uptake
Stimulates ketoacid production

TABLE 3. Other counter-regulatory hormones

Catecholamines (released by the adrenal glands)
• Inhibit insulin release (alpha adrenergic) • Stimulate glucagon release • Stimulate liver gluconeogenesis
Cortisol (released by the adrenal glands)
• Inhibits insulin release • Stimulates liver gluconeogenesis • Inhibits glucose uptake in muscle and adipose tissue
Growth hormone (released by the pituitary gland)
• Inhibits insulin action • Stimulates lipolysis

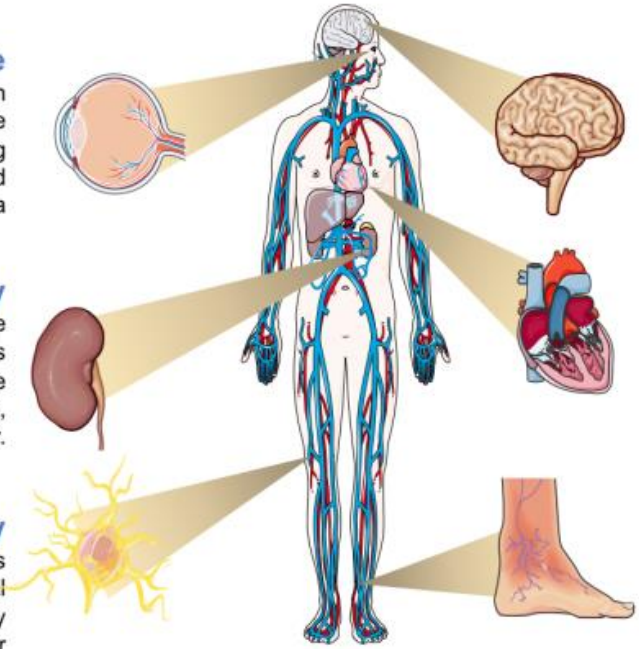
Major Complications of Diabetes

Microvascular

Eye
High blood glucose and high blood pressure can damage eye blood vessels, causing retinopathy, cataracts and glaucoma

Kidney
High blood pressure damages small blood vessels and excess blood glucose overworks the kidneys, resulting in nephropathy.

Neuropathy
Hyperglycemia damages nerves in the peripheral nervous system. This may result in pain and/or numbness. Feet wounds may go undetected, get infected and lead to gangrene.



Macrovascular

Brain
Increased risk of stroke and cerebrovascular disease, including transient ischemic attack, cognitive impairment, etc.

Heart
High blood pressure and insulin resistance increase risk of coronary heart disease

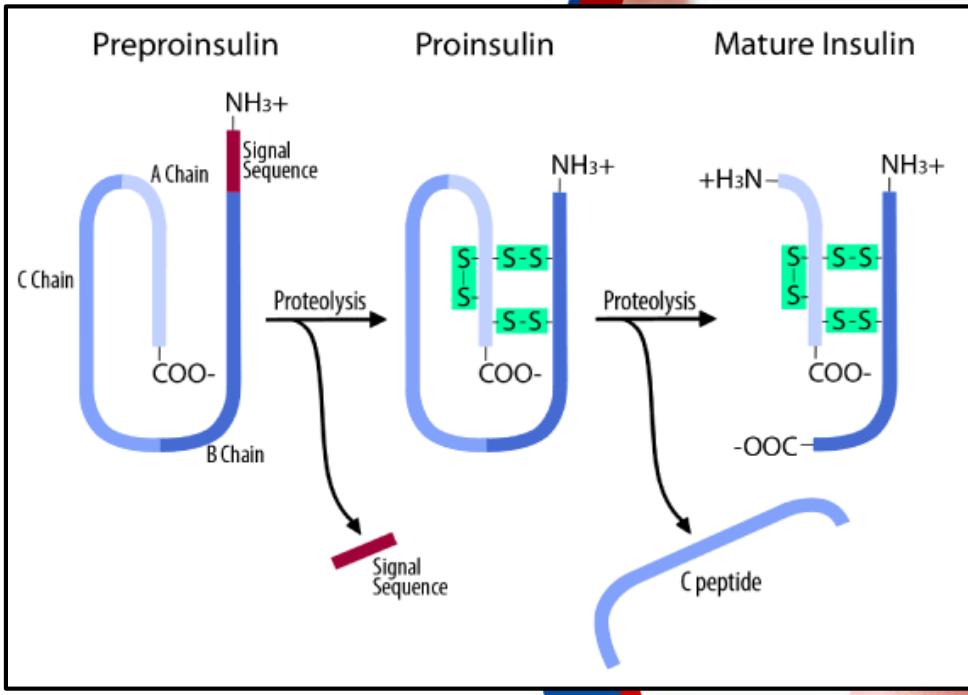
Extremities
Peripheral vascular disease results from narrowing of blood vessels increasing the risk for reduced or lack of blood flow in legs. Feet wounds are likely to heal slowly contributing to gangrene and other complications.

History: Treatment of Diabetes by Diet

- Egypt 3500 BC; India 2500 BC
- John Rollo, MD (Scotland) –recommended low carbohydrate meat diet to reduce glucosuria
- 1919 Dr. Frederick Allen (Rockefeller Institute in New York) published his “Total Dietary Regulations in the Treatment of Diabetes”
  - Introduced a therapy of strict dieting/ starvation treatment – as a way to manage diabetes with Total Carbohydrate restriction and caloric restriction (400 cal/day)
  - Eliminated glucosuria
  - Difficult to follow! Fell out of favor with discovery of insulin
- Also championed Low Salt diet for hypertension
- Later, diet treatment was validated by Dr. E.P. Joslin

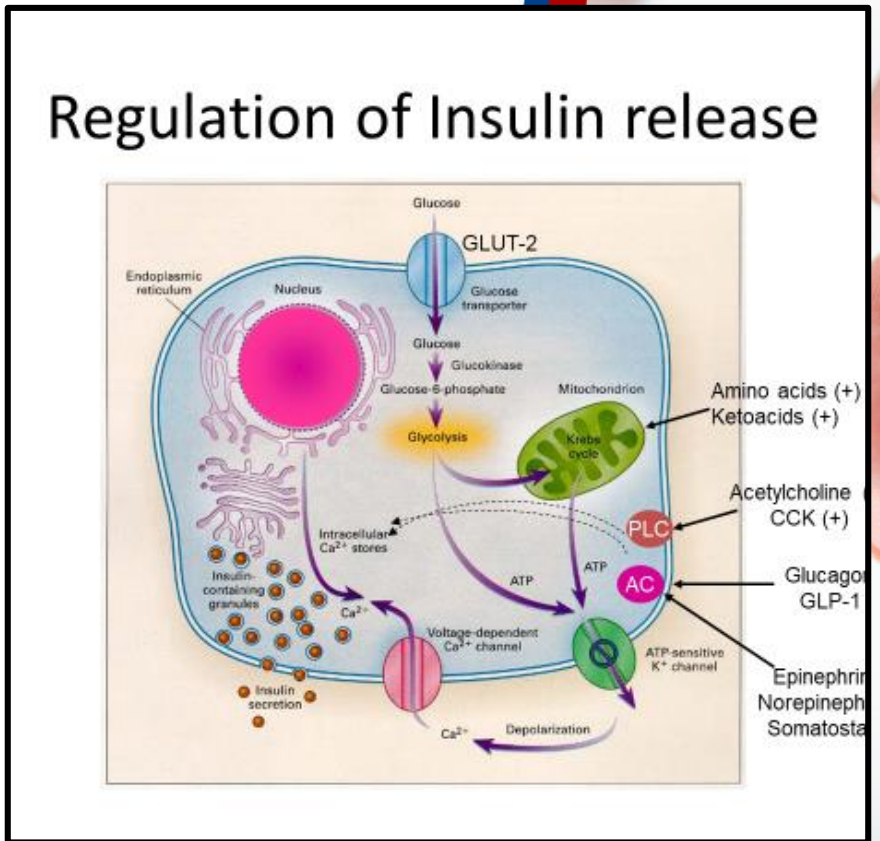
Insulin

- Insulin is a peptide hormone synthesized from pre-proinsulin
- Pre-proinsulin undergoes posttranslational modification in the endoplasmic reticulum to form proinsulin
- The active form of insulin is formed by cleavage of the c-peptide chain linking the alpha and beta chains of proinsulin
- Both insulin and c-peptide are packaged in secretory granules and are co-released in response to glucose stimulation
- No c-peptide in T1 DM



Review –regulation of insulin secretion

- Insulin synthesis and secretion are increased by glucose, amino acids, and gastrointestinal hormones (incretins such as glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).
- Of these glucose is the most important stimulus for insulin release.
- During periods of stress epinephrine inhibits insulin release to allow for mobilization of stored energy fuels.
- Scarcity of dietary fuels also results in a decrease in insulin secretion as there is a lack of secretory stimuli.



Discovery of Insulin

- 1889 - Oskar Minkowski and Joseph von Mering
  - when the pancreas gland was removed from dogs, the animals developed symptoms of diabetes and died soon afterward.
  - the idea that the pancreas was the site where “pancreatic substances” (insulin) were produced.
  - Later experimenters Paul Langerhans narrowed this search to the islets of Langerhans (clusters of specialized cells in the pancreas).

Discovery of Insulin

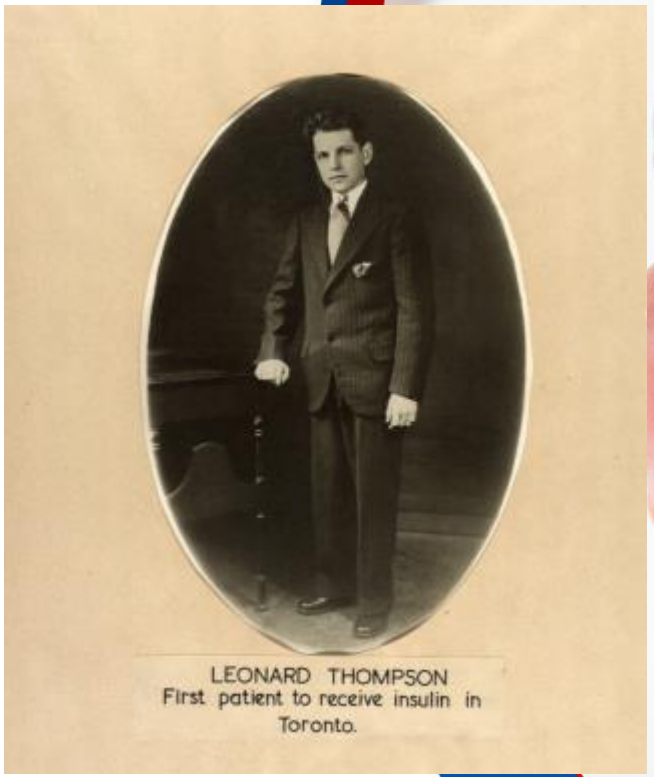
- 1910 Sir Edward Albert Sharpey-Shafer, Physiologist, “Founder of Endocrinology”
  - suggested only one chemical was missing from the pancreas in people with diabetes
  - called this chemical insulin, which comes for the Latin word *insula,* meaning “island”
  - He was also the co-discover of Adrenaline; “ductless glands” and internal secretion and the Prone pressure method of artificial respiration in asphyxia and drowning

Discovery of Insulin – successful isolation from dogs

- Banting and Best
- Working in lab of John MacCleod in Toronto
- Used pancreatic extract to treat dogs with pancreas removed for 70 days (ran out of extract)
- Biochemistry colleague James Collip Isolated & purified insulin from extracts

First treatment with insulin

- January 11, 1922
- 14-year-old Leonard Thompson became the first person to receive an insulin injection as a treatment for diabetes
- Prior to that, people with Type 1 diabetes did not survive
- Nobel Prize 1923 to Banting and McCleod



Insulin manufacture

- Scientists “sold” their patent to the university of Toronto for $1 each
- Eli Lily started large scale production of Insulin (purified from animal pancreas extracts)
- Frederick Sanger – first to sequence the Amino acids of insulin (Nobel Prize, 1958)
- Dorothy Hodgkin – crystal structure of insulin

E.P. Joslin. M.D.

- First Dr. in the U.S. to specialize in Diabetes
- From the beginning of his career, kept a registry of his diabetes patients
- Carried out extensive metabolic studies examined fasting and feeding in patients with varying severities of diabetes –validating the benefit of carbohydrate and calorie restriction diets
- Educated generations of doctors & nurses as well as patients and families
  - Careful monitoring of diabetes that rendered good control would allow the patient to avoid chronic complications of diabetes along with prevention of acute acidosis
- Wrote the first medical textbook and patient handbook on Diabetes
- His practice became the first Diabetes center in the world

Some words of wisdom!

- "(Diabetologic) Education is not a part of the treatment of diabetes, it is the treatment.“
- "The man who gives up an active outdoor life and is promoted to an office chair by this change becomes a promising candidate for diabetes.“
- "The diabetic who knows the most, lives the longest."

Diabetic Creed in the *Patient Manual*

- *Three horses draw the diabetic chariot and their names are diet, exercise and insulin. In fact, all of us in our life's journey depend on the three, but seldom recognize the third although we often realize we are poor charioteers. Yet we fortunate ones have instinct to help us hold the reins, but the diabetic cannot trust his instincts as a guide, and in place of it must depend upon dieticians, nurses and doctors unless he understands his disease.*

Synthetic Human Insulin – Recombinant Technology 1978

- FDA approved in 1982 (partnered with Eli Lily)
- David Goeddel & colleagues (Genentech) – world's first biotechnology company
- Expressed Insulin A & B chains in E coli – (cloning) – can get large amount and purify the protein
- On the WHO Model List of Essential Medicines

Types of Diabetes

- Type 1
- Type 2
- Gestational
- Others (many!)
- Pre-Diabetes

Diagnosis of Diabetes

Table 2.2—Criteria for the diagnosis of diabetes
FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

Fasting Plasma Glucose Test

No food or drink
8 to 12 hours
prior to test

Blood is drawn and
tested for the level
of glucose in blood

High glucose level = potential diabetes

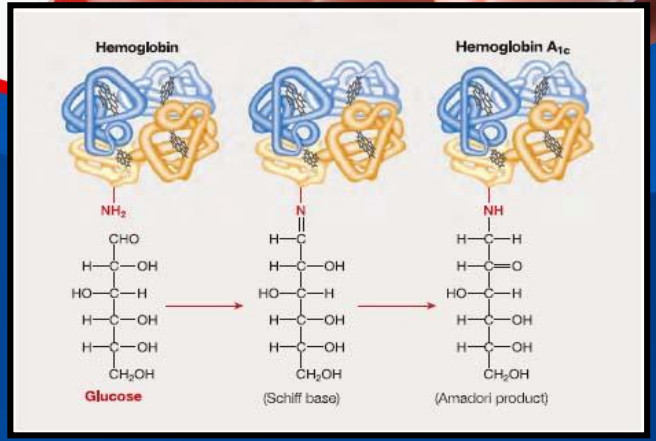
A.D.A.M.

Oral Glucose Tolerance Test (OGTT)

- Adequate carbohydrate intake (at least 150 g/day should be assured for 3 days prior to OGTT

Hemoglobin A1C (A1C)

- Glycated hemoglobin fraction - amount of hemoglobin with glucoses attached
- Used to measure of overall glycemic control in patients with diabetes over time (120 days –life of RBC)
- Useful because can be done anytime; no need to fast
- Added to diagnostic criteria in 2010 by the ADA
- **HgA1c ≥ 6.5% for diagnosis**
- More costly than FPG
- **HgA1c > 6.5% for diagnosis**
- Many abbreviations for Hemoglobin A1c - HbA1c; HgA1c A1c; HGBA1C



Hemoglobin A1C

- When there is discordance between A1C and FPG, FPG is more accurate
- Factors that may impact glycation independent of glycemia
  - Hemodialysis
  - Pregnancy
  - HIV treatment
  - Age
  - Ethnicity
  - Anemia
  - Hemoglobinopathies

Who should be screened

Table 2.3—Criteria for screening for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in adults with overweight or obesity (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) who have one or more of the following risk factors:
   - First-degree relative with diabetes
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - History of CVD
   - Hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - Women with polycystic ovary syndrome
   - Physical inactivity
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. Patients with prediabetes (A1C ≥5.7% [39 mmol/mol], IGT, or IFG) should be tested yearly.
3. Women who were diagnosed with GDM should have lifelong testing at least every 3 years.
4. For all other patients, testing should begin at age 35 years.
5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.
6. People with HIV

CVD, cardiovascular disease; GDM, gestational diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

New recommendation 2022

- For all people, screening should begin at **age 35**

Type 1 Diabetes

- Formerly Juvenile Diabetes
- Pathogenesis: Autoimmune β cell destruction in the pancreas leading to a lack of insulin production
- REQUIRES INSULIN TREATMENT
- Most common type of Diabetes BEFORE the discovery and wide use of insulin

Pathophysiology of T1DM

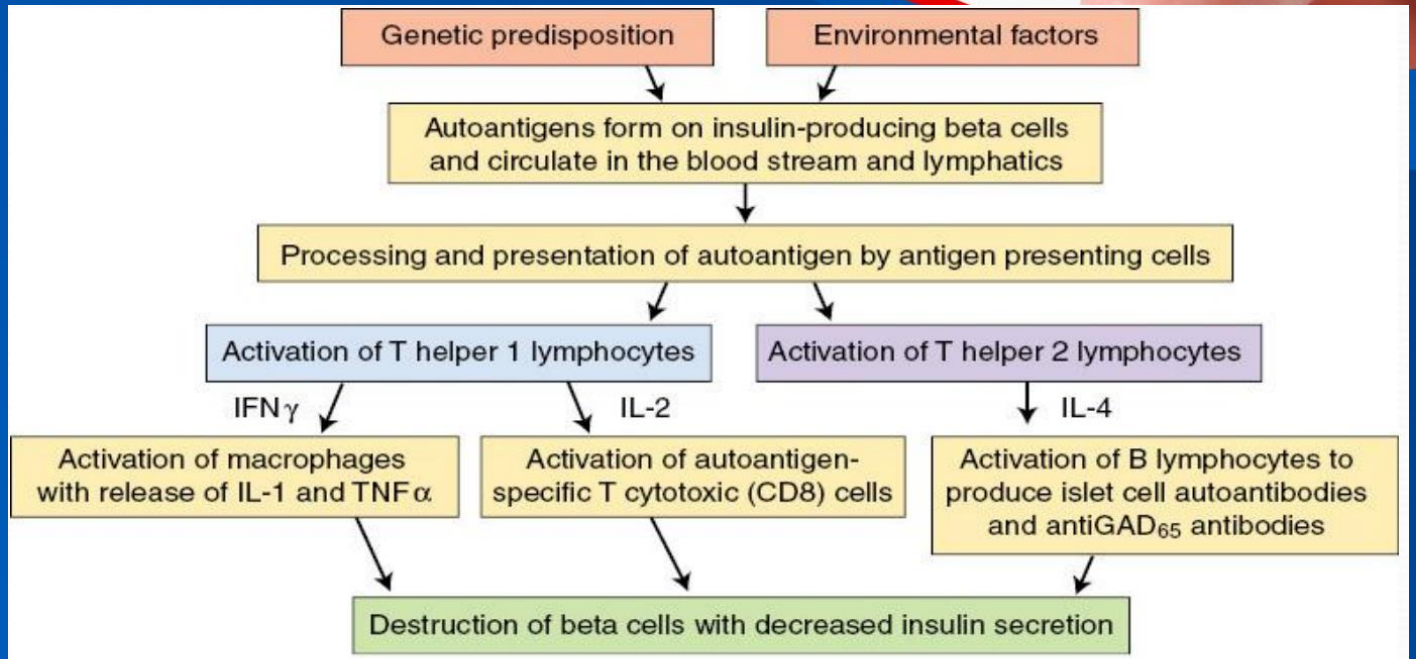
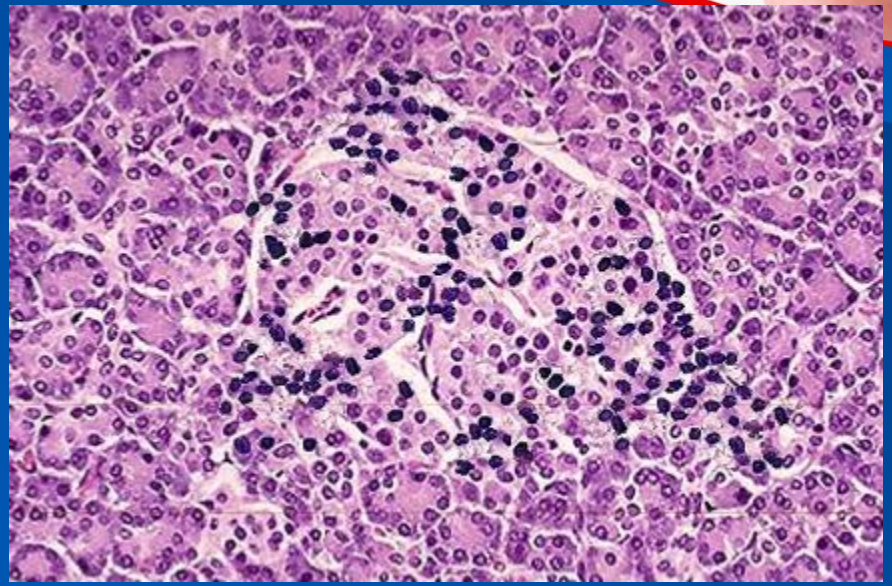


Figure 21-13 Pathophysiology of type 1 diabetes mellitus. *GAD_{65}*, glutamic acid decarboxylase; *INF*-γ Interferon-gamma; *IL*, interleukin; *TNF*-α, tumor necrosis factor-alpha.

Histology



Symptoms of T1DM

- Feeling more thirsty than usual (polydipsia)
- Urinating a lot; bed-wetting in children who have never wet the bed during the night (polyuria)
- Feeling very hungry (polyphagia)
- Losing weight without trying
- Feeling irritable or having other mood changes
- Feeling tired and weak
- Having blurry vision
- Symptoms for only several days or several weeks; may present abruptly (ketoacidosis) hyperglycemia, acidosis, and ketosis
- Beta cell destruction starts months or years before clinical symptoms

Clinical Signs in T1DM

System	Symptom/Physical Exam
Central	Polydipsia, Polyphagia, Lethargy, Fatigue, **Acute Confusion**
Systemic	Weight Loss
Respiratory	**Kussmaul Breathing, Hyperventilation**
EENT	Blurred Vision, **Smell Acetone**
Cardiovascular	Tachycardia
Gastrointestinal	**Nausea, Vomiting, Abdominal Pain**
Gastrourinary	Polyuria, Glycosuria, Nocturia, **Ketonuria**
Musculoskeletal	**Muscle Wasting**

Self Monitoring of Plasma Glucose (SMPG)

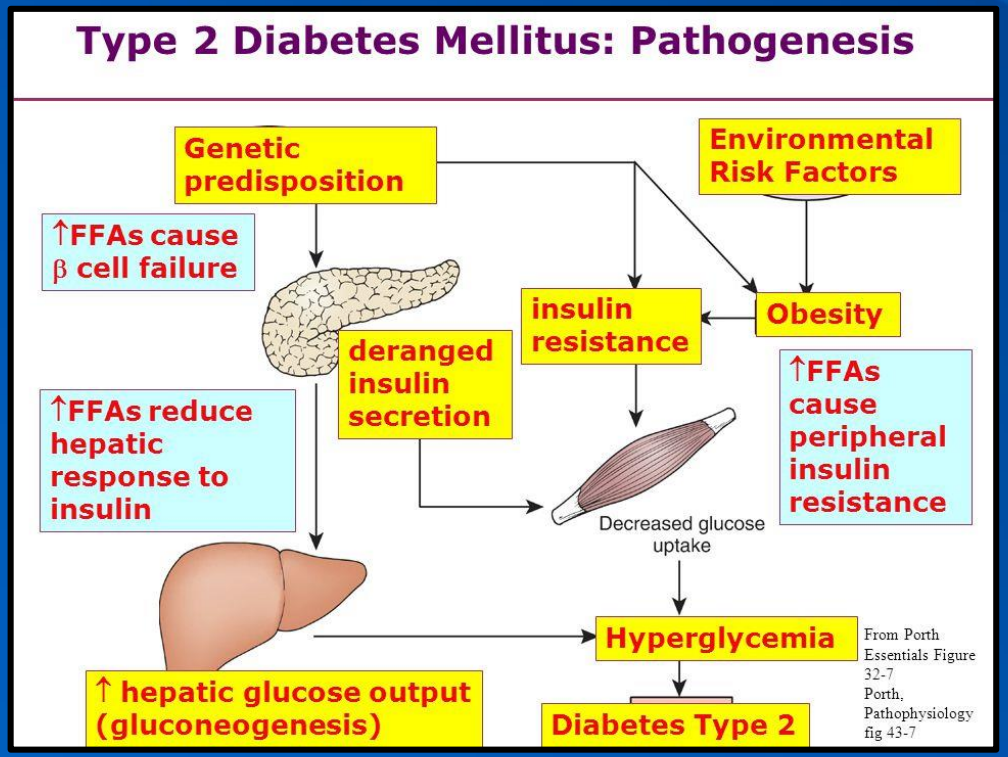
Blood Glucose Monitoring (BGM) (updated terminology 2022

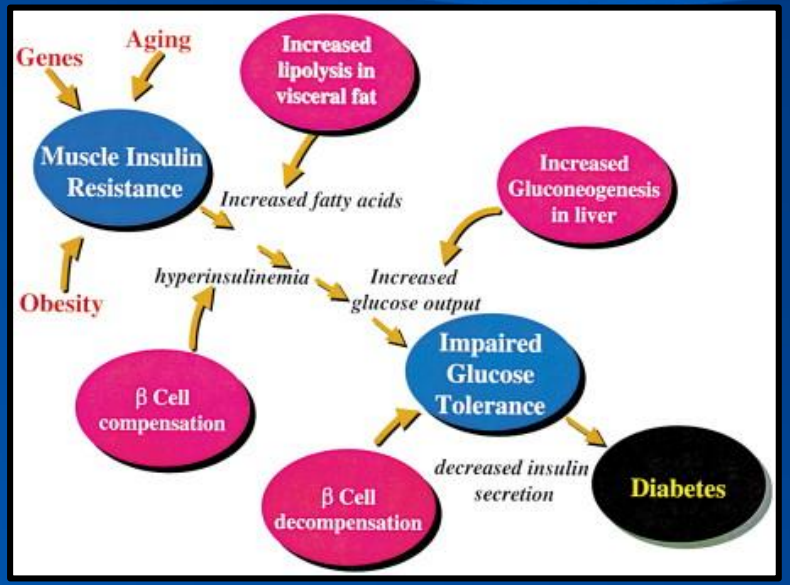
Home testing by glucometer

Continuous Glucose Monitoring (CGM)

Combined CGM and insulin pump

Type 2 DM


Type 2 Diabetes Mellitus: Pathogenesis
Genetic predisposition
Environmental Risk Factors
↑FFAs cause β cell failure
insulin resistance
Obesity
deranged insulin secretion
↑FFAs cause peripheral insulin resistance
↑FFAs reduce hepatic response to insulin
Decreased glucose uptake
Hyperglycemia
↑ hepatic glucose output (gluconeogenesis)
Diabetes Type 2
From Porth Essentials Figure 32-7
Porth, Pathophysiology fig 43-7


Genes
Aging
Increased lipolysis in visceral fat
Muscle Insulin Resistance
Increased fatty acids
Increased Gluconeogenesis in liver
Obesity
hyperinsulinemia
Increased glucose output
β Cell compensation
Impaired Glucose Tolerance
β Cell decompensation
decreased insulin secretion
Diabetes

Diagnosis of Diabetes

Table 2.2—Criteria for the diagnosis of diabetes
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OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

Type 2 Diabetes

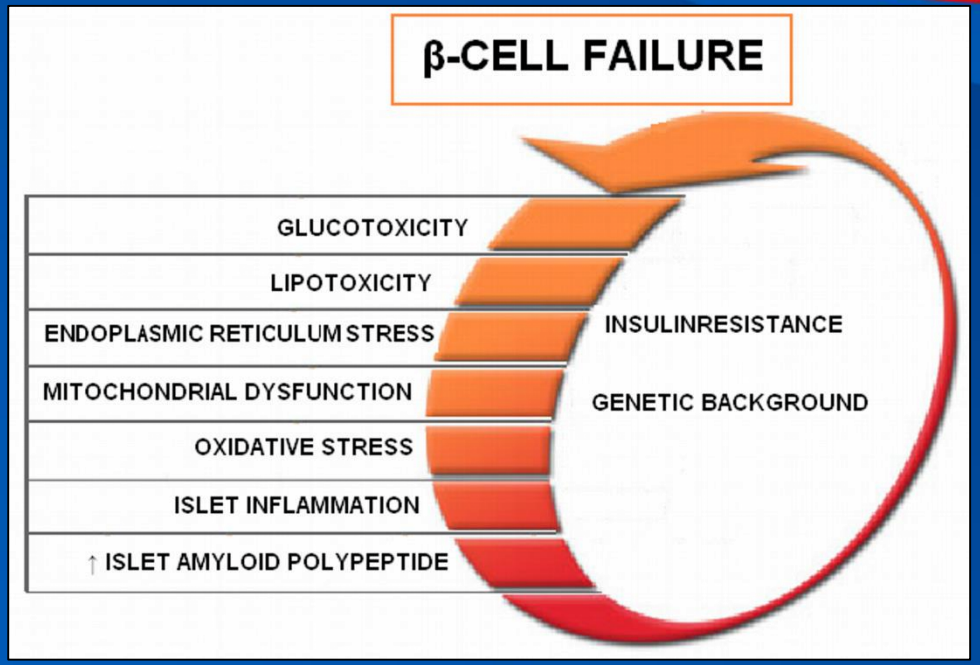
- Hyperglycemia without symptoms is present for a long time
- Accounts for 90% of diabetes
- Subtle onset, mild symptoms, develops gradually
- Most are > 40 year old, Familial
- Minorities disproportionally effected
- Obesity, physical inactivity, inflammation produce insulin resistance
- Resistance to insulin action; pancreas compensates by releasing more and more insulin to correct hyperglycemia. Eventually, compensatory insulin secretion becomes inadequate.

- May eventually require insulin for treatment

Insulin resistance

- Insulin resistance is a physiological condition in which cells fail to respond to the normal actions of the hormone insulin
- The body produces insulin, but the cells in the body become resistant to insulin and are unable to use it as effectively, leading to hyperglycemia
- Beta cells in the pancreas subsequently increase their production of insulin, further contributing to hyperinsulinemia
- At some point the Beta cells fail and no insulin is produced

Beta cell failure in T2DM multiple proposed causes



Progression of T2 DM

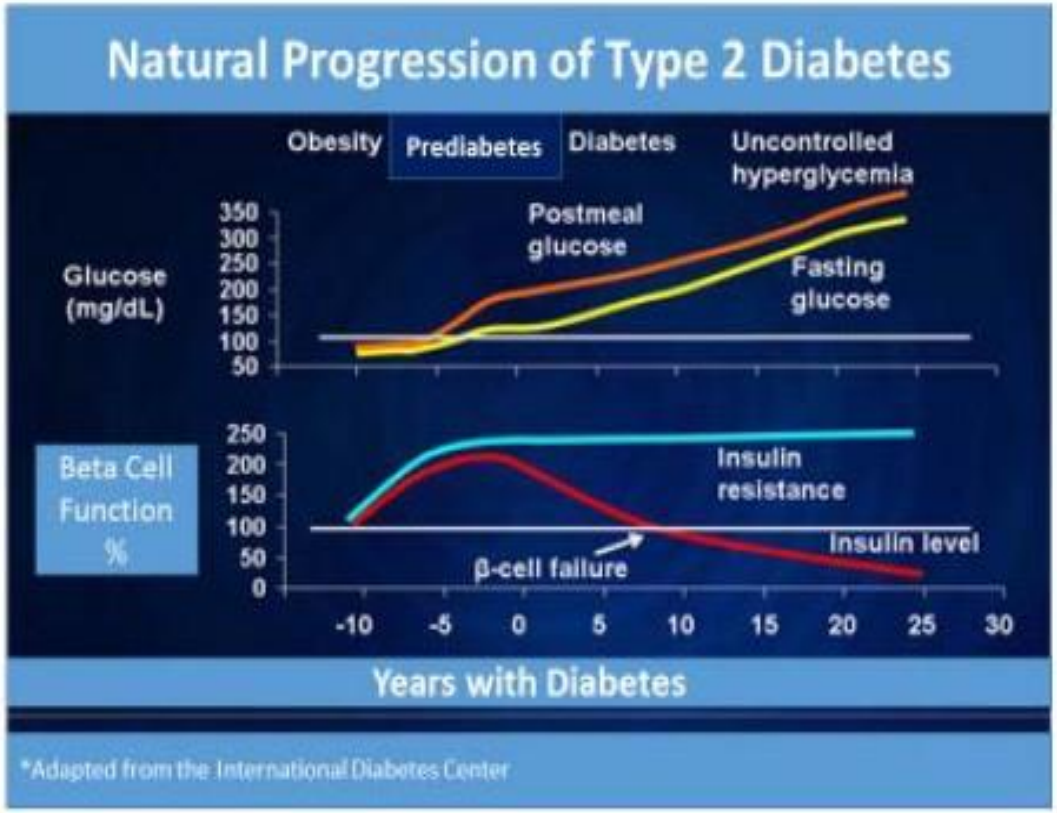
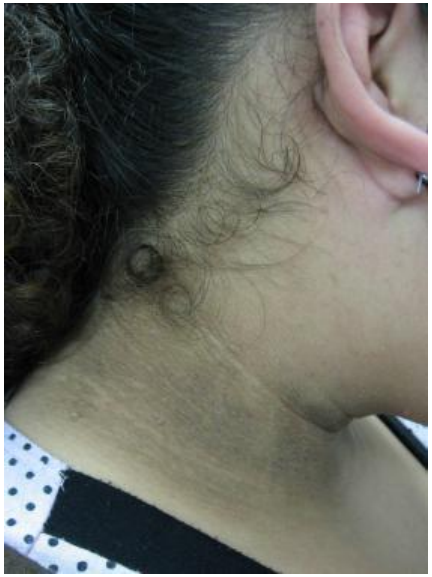


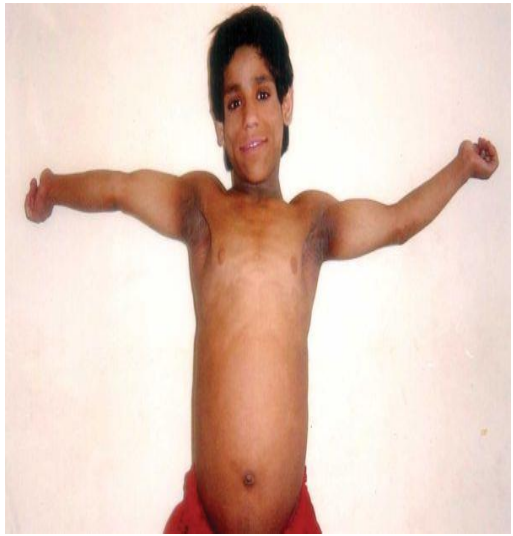
Table 6.3—Summary of glycemic recommendations for many nonpregnant adults with diabetes

A1C	<7.0% (53 mmol/mol)*#
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

*More or less stringent glycemic goals may be appropriate for individual patients. #CGM may be used to assess glycemic target as noted in Recommendation 6.5b and **Fig. 6.1**. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations (as per **Fig.6.2**). †Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

Acanthosis Nigricans hyperpigmentation- a clinical sign of Insulin Resistance

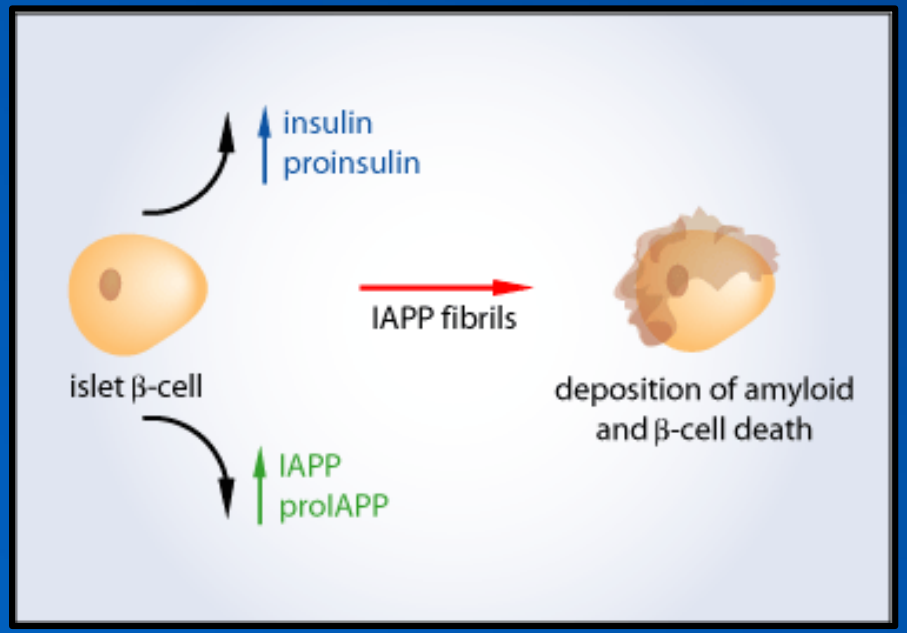


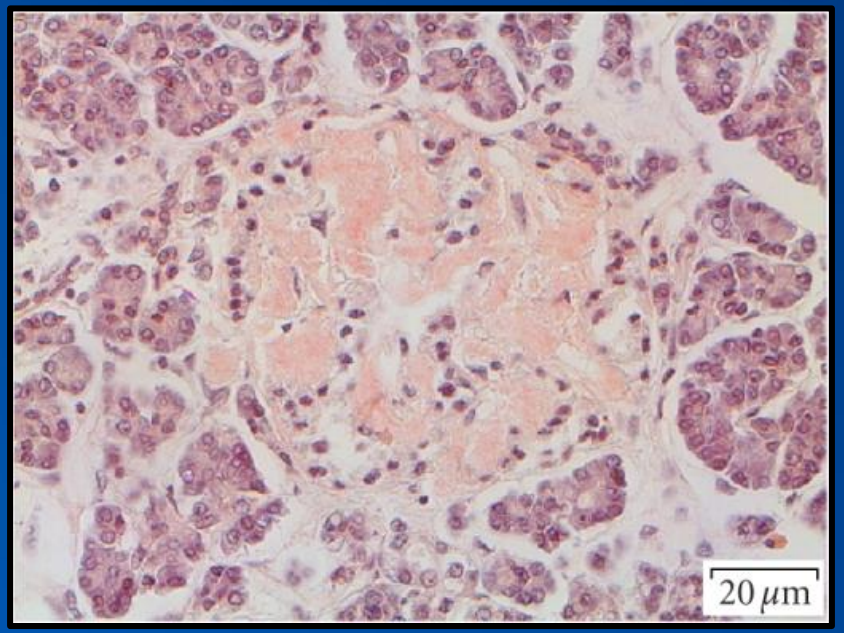


- NOT seen in T1DM

T 2 DM pancreas histology

Islet amyloid → β cell dysfunction



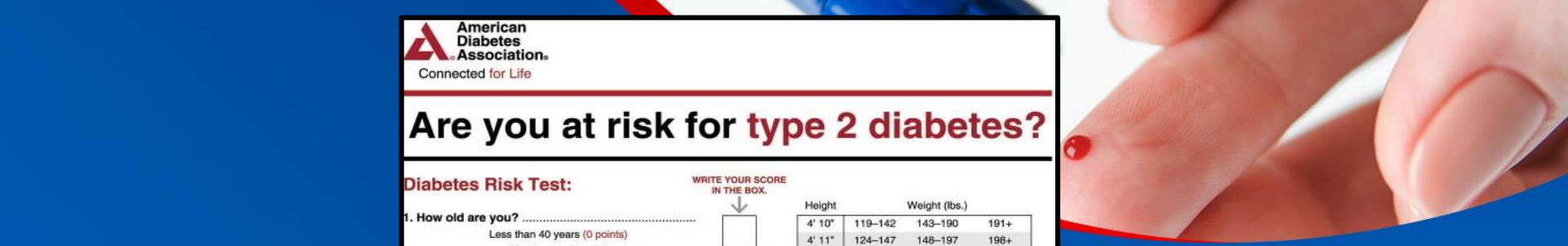


Pre-diabetes: Increased risk for diabetes

- Patient is higher than normal but not at diagnostic levels for T2DM:
  - FPG 100-125 mg/dL
  - OGTT 140-199 mg/dL
  - A1c 5.7-6.4%
- These numbers are one of the qualifying features of the Metabolic Syndrome

Table 2.4—Categories of increased risk for diabetes (prediabetes)*
FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
OR
A1C 5.7–6.4% (39–47 mmol/mol)

*For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.



American Diabetes Association.
Connected for Life

Are you at risk for type 2 diabetes?

Diabetes Risk Test:

WRITE YOUR SCORE IN THE BOX.

1. How old are you?
Less than 40 years (0 points)
40–49 years (1 point)
50–59 years (2 points)
60 years or older (3 points)

2. Are you a man or a woman?
Man (1 point) Woman (0 points)

3. If you are a woman, have you ever been diagnosed with gestational diabetes?
Yes (1 point) No (0 points)

4. Do you have a mother, father, sister or brother with diabetes?
Yes (1 point) No (0 points)

5. Have you ever been diagnosed with high blood pressure?
Yes (1 point) No (0 points)

6. Are you physically active?
Yes (0 points) No (1 point)

7. What is your weight category?
See chart at right.

Height	Weight (lbs.)		
4' 10"	119–142	143–190	191+
4' 11"	124–147	148–197	198+
5' 0"	128–152	153–203	204+
5' 1"	132–157	158–210	211+
5' 2"	136–163	164–217	218+
5' 3"	141–168	169–224	225+
5' 4"	145–173	174–231	232+
5' 5"	150–179	180–239	240+
5' 6"	155–185	186–246	247+
5' 7"	159–190	191–254	255+
5' 8"	164–196	197–261	262+
5' 9"	169–202	203–269	270+
5' 10"	174–208	209–277	278+
5' 11"	179–214	215–285	286+
6' 0"	184–220	221–293	294+
6' 1"	189–226	227–301	302+
6' 2"	194–232	233–310	311+
6' 3"	200–239	240–318	319+
6' 4"	205–245	246–327	328+
	1 point	2 points	3 points

If you weigh less than the amount in the left column: 0 points

Adapted from Bang et al., Ann Intern Med 151:775–783, 2009 • Original algorithm was validated without gestational diabetes as part of the model.

ADD UP YOUR SCORE.

If you scored 5 or higher:

You are at increased risk for having type 2 diabetes. However, only your doctor can tell for sure if you do have type 2 diabetes or prediabetes, a condition in which blood glucose levels are higher than normal but not yet high enough to be diagnosed as diabetes. Talk to your doctor to see if additional testing is needed.

Type 2 diabetes is more common in African Americans, Hispanics/Latinos, Native Americans, Asian Americans, and Native Hawaiians and Pacific Islanders.

Higher body weight increases diabetes risk for everyone. Asian Americans are at increased diabetes risk at lower body weight than the rest of the general public (about 15 pounds lower).

Lower Your Risk

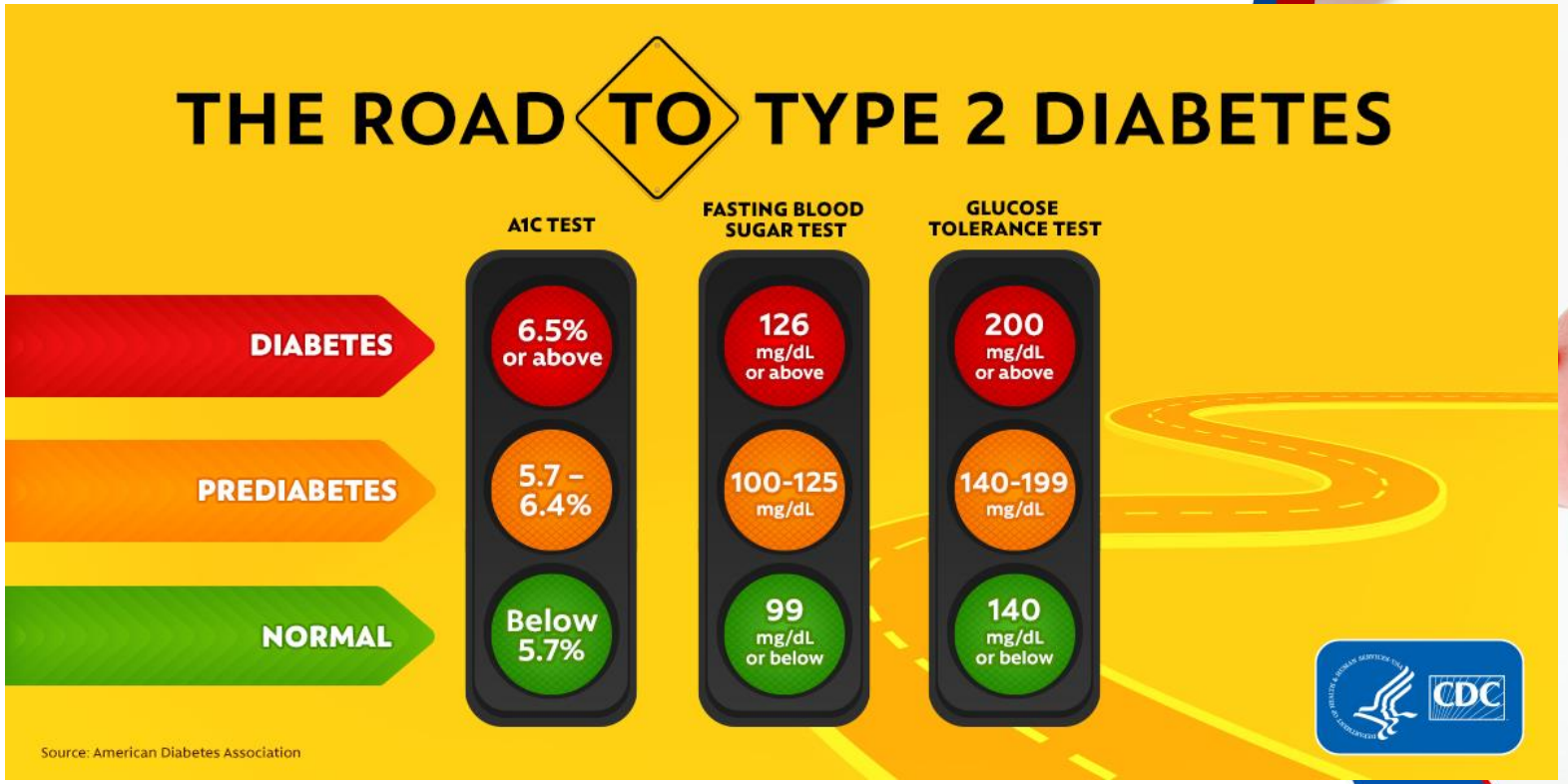
The good news is you can manage your risk for type 2 diabetes. Small steps make a big difference in helping you live a longer, healthier life.

If you are at high risk, your first step is to visit your doctor to see if additional testing is needed.

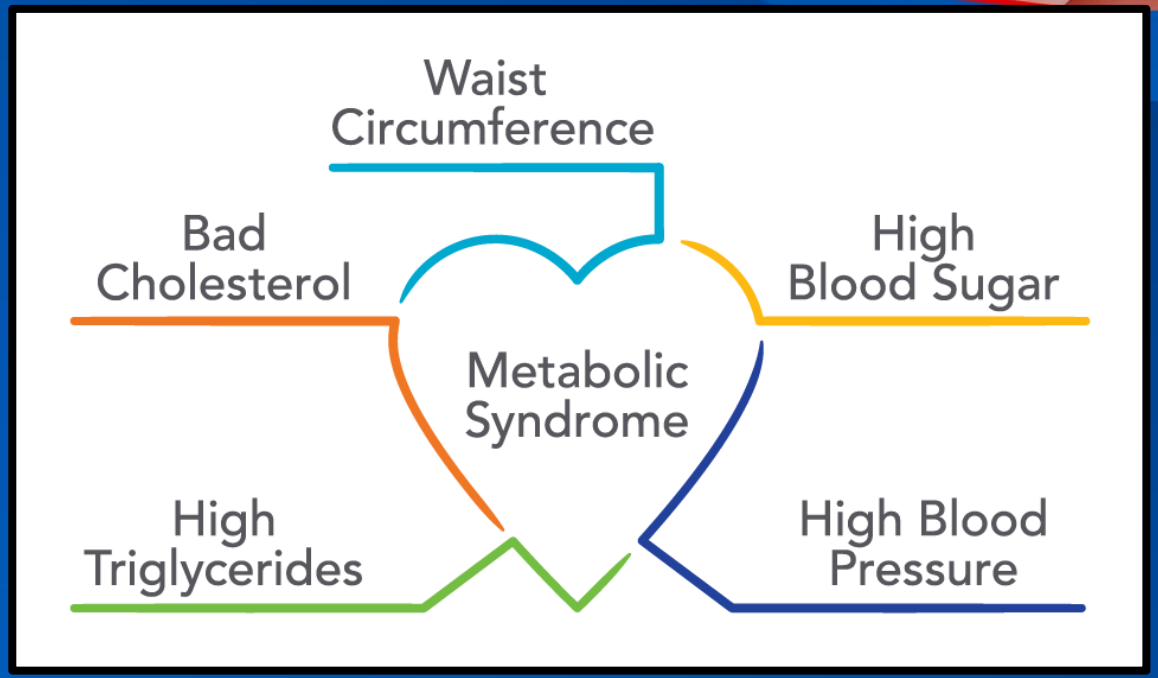
Visit diabetes.org or call 1-800-DIABETES (800-342-2383) for information, tips on getting started, and ideas for simple, small steps you can take to help lower your risk.

Learn more at diabetes.org/risktest | 1-800-DIABETES (800-342-2383)

Pre-Diabetes



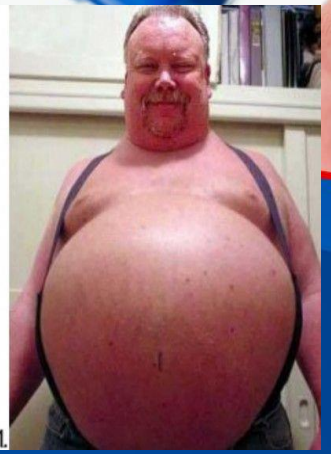
Pre-Diabetes is part of Metabolic Syndrome




BAD HABITS
and unhealthy lifestyle
SWEETS
JUNK FOOD
REST AT HOME
UNHEALTHY DRINKS

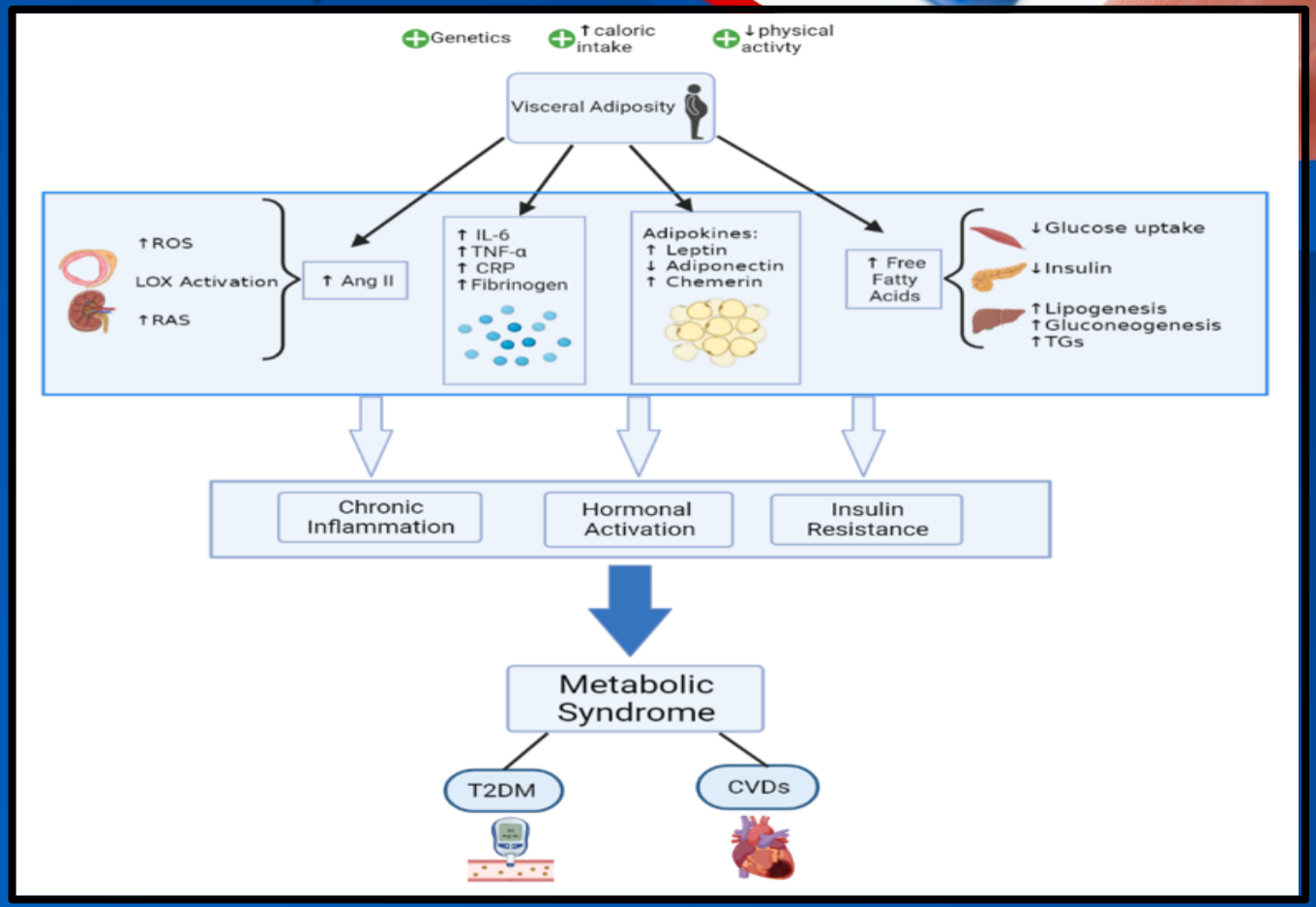
The Metabolic Syndrome

Any
3 out of 5



Central Obesity: Waist circumference > 40 inches for men; > 35 inches for women
Elevated blood pressure: >130/80 OR taking medicine for high blood pressure
High triglycerides: > 150 mg/dL fasting or taking medication for high triglycerides
Low HDL cholesterol or taking medication for low HDL cholesterol:
Men < 40 mg/dL; Women < 50 mg/dL
Fasting glucose > 100 mg/dL or taking medication for high blood glucose

Metabolic Syndrome



Gestational Diabetes Mellitus (GDM)

- Hyperglycemia occurring at 24-28 weeks gestation
- Clinical recognition is important since therapy can reduce perinatal morbidity and mortality

Gestational Diabetes

- Priscilla White, M.D.
- A founding member of the Joslin Diabetes Center; Pioneer in the treatment in diabetes during pregnancy
- (1949) White Classification of Diabetic Pregnancies – basis for what is used today
- Showed the importance of strict glucose control during pregnancy
- When she started, fetal success rate was 54%, when she retired in 1974, it was >90%

Diabetes in Pregnancy

- Screen for undiagnosed type 2 diabetes at the first prenatal visit, in THOSE WITH RISK FACTORS* , using the standard diagnostic criteria. If mom is positive for any of the criteria, and it's repeated on a separate day, she has Diabetes.

- In pregnant women who do not have diabetes, screen for GDM @ 24-28 weeks of gestation, using one of the two types of OGTT and the diagnostic cut points for GDM. (next slide)

- Screen women with GDM for persistent diabetes 4 - 12 weeks postpartum.

- Women with history of GDM should have lifelong screening for development of Diabetes or Prediabetes at least every 3 years.

GDM OGTT dx values

More stringent than Dx of DM
Strict control = better outcomes

Table 2.6—Screening for and diagnosis of GDM

One-step strategy

Perform a 75-g OGTT, with plasma glucose measurement when patient is fasting and at 1 and 2 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes.

The OGTT should be performed in the morning after an overnight fast of at least 8 h.

The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

- Fasting: 92 mg/dL (5.1 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 153 mg/dL (8.5 mmol/L)

Two-step strategy

Step 1: Perform a 50-g GLT (nonfasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes.

If the plasma glucose level measured 1 h after the load is ≥130 mg/dL, 135 mg/dL, or 140 mg/dL* (7.2 mmol/L, 7.5 mmol/L, or 7.8 mmol/L), proceed to a 100-g OGTT.

Step 2: The 100-g OGTT should be performed when the patient is fasting.

The diagnosis of GDM is made if at least two of the following four plasma glucose levels (measured fasting and 1 h, 2 h, 3 h after the OGTT) are met or exceeded:

	Carpenter/Coustan (59)	or	NDDG (60)
• Fasting	95 mg/dL (5.3 mmol/L)		105 mg/dL (5.8 mmol/L)
• 1 h	180 mg/dL (10.0 mmol/L)		190 mg/dL (10.6 mmol/L)
• 2 h	155 mg/dL (8.6 mmol/L)		165 mg/dL (9.2 mmol/L)
• 3 h	140 mg/dL (7.8 mmol/L)		145 mg/dL (8.0 mmol/L)

NDDG, National Diabetes Data Group. *The ACOG recommends either 135 mg/dL (7.5 mmol/L) or 140 mg/dL (7.8 mmol/L). A systematic review determined that a cutoff of 130 mg/dL (7.2 mmol/L) was more sensitive but less specific than 140 mg/dL (7.8 mmol/L) (55).

Complications of GDM

- Macrosomic baby or LGA (large for gestational age) >4000g; 8lb 13oz: birth trauma to baby & mom - making C section necessary
- Macrosomic infants are at higher risk for intrauterine death
- Macrosomic infants are at higher risk for hypoglycemia in the perinatal period and developing type 2 Diabetes later in life
- Mother with GDM has greater risk of developing type 2 Diabetes later as does the baby
- Hyperglycemia may increase risk of early labor and respiratory distress syndrome and neonatal hypoglycemia

Treatments for Diabetes

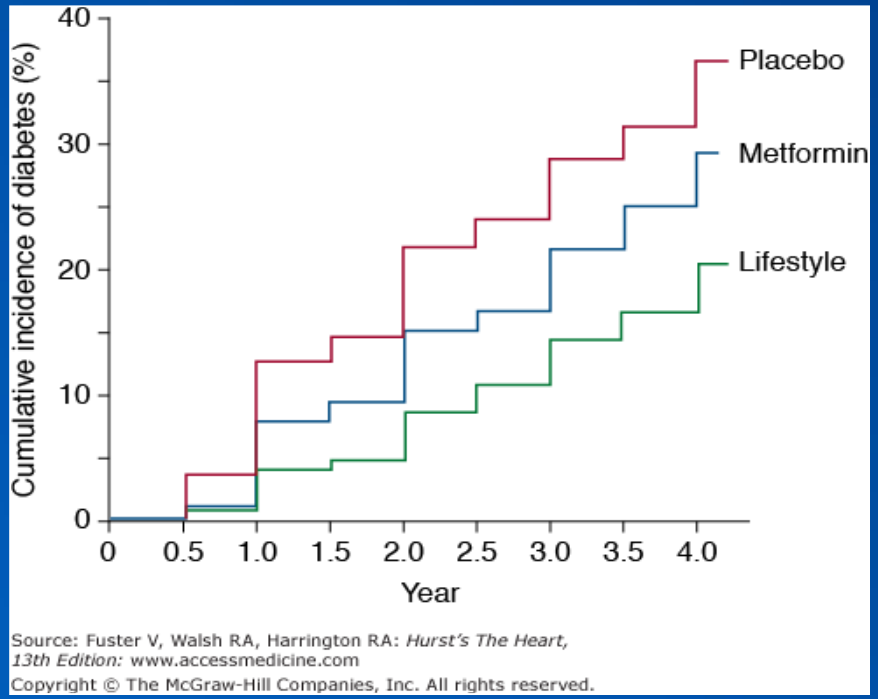
- Insulin – necessary for T1 and may become necessary for T2
- Lifestyle modification
- Other Classes of drugs – oral and injectables
- Bariatric Surgery
- Stem cell transplant

Insulin

- Absolute requirement for T1 DM
- Control is important – too much insulin can lead to hypoglycemia
- Defensive increase in calorie intake caused by the fear or experience of hypoglycemia can cause weight gain
- Insulin therapy or intensification of insulin therapy commonly results in weight gain in both type 1 and type 2 diabetes
- With insulin, glucose enters the cells, and excess glucose will be converted into fat

Lifestyle Modification for Prediabetes

- Lifestyle modification* treatment of pre-diabetes and diabetes



↓31%

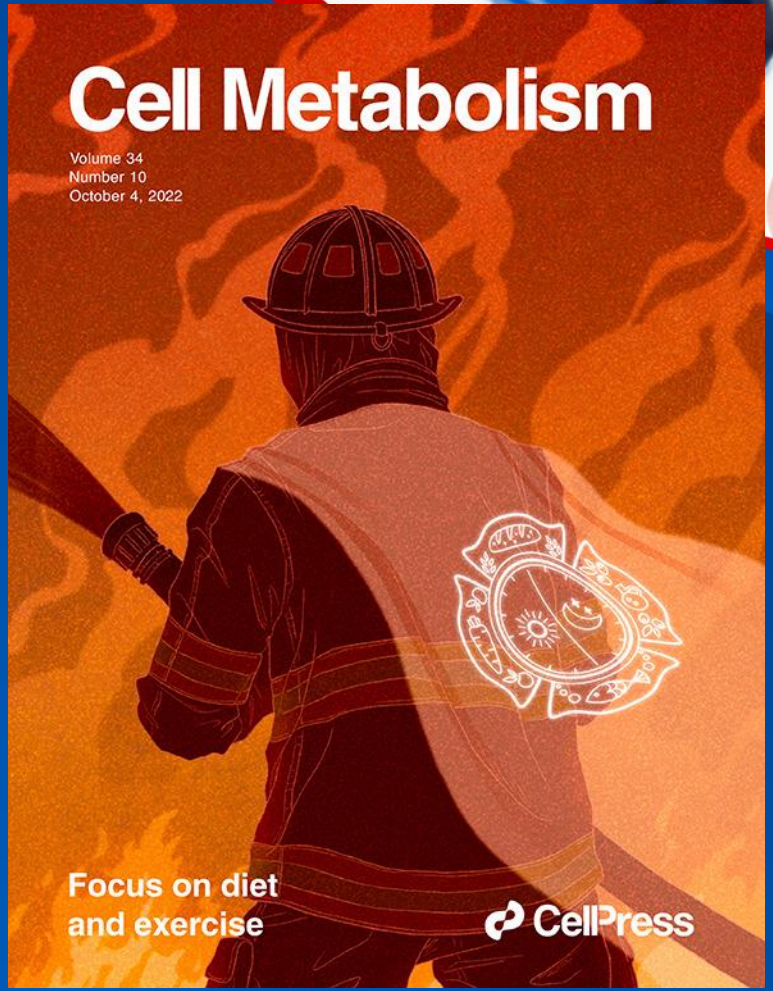
↓58%

NEJM 346:393;2002

Lifestyle Modification
Eat less; move more

Lifestyle modifications
Diet

- Avoid refined carbohydrates
- Cut back on sugar
- Reduce portion size
- Eat “healthier” foods
- Drink less alcohol
- Sleep is important too!


Cell Metabolism
Volume 34
Number 10
October 4, 2022
Focus on diet
and exercise
CellPress

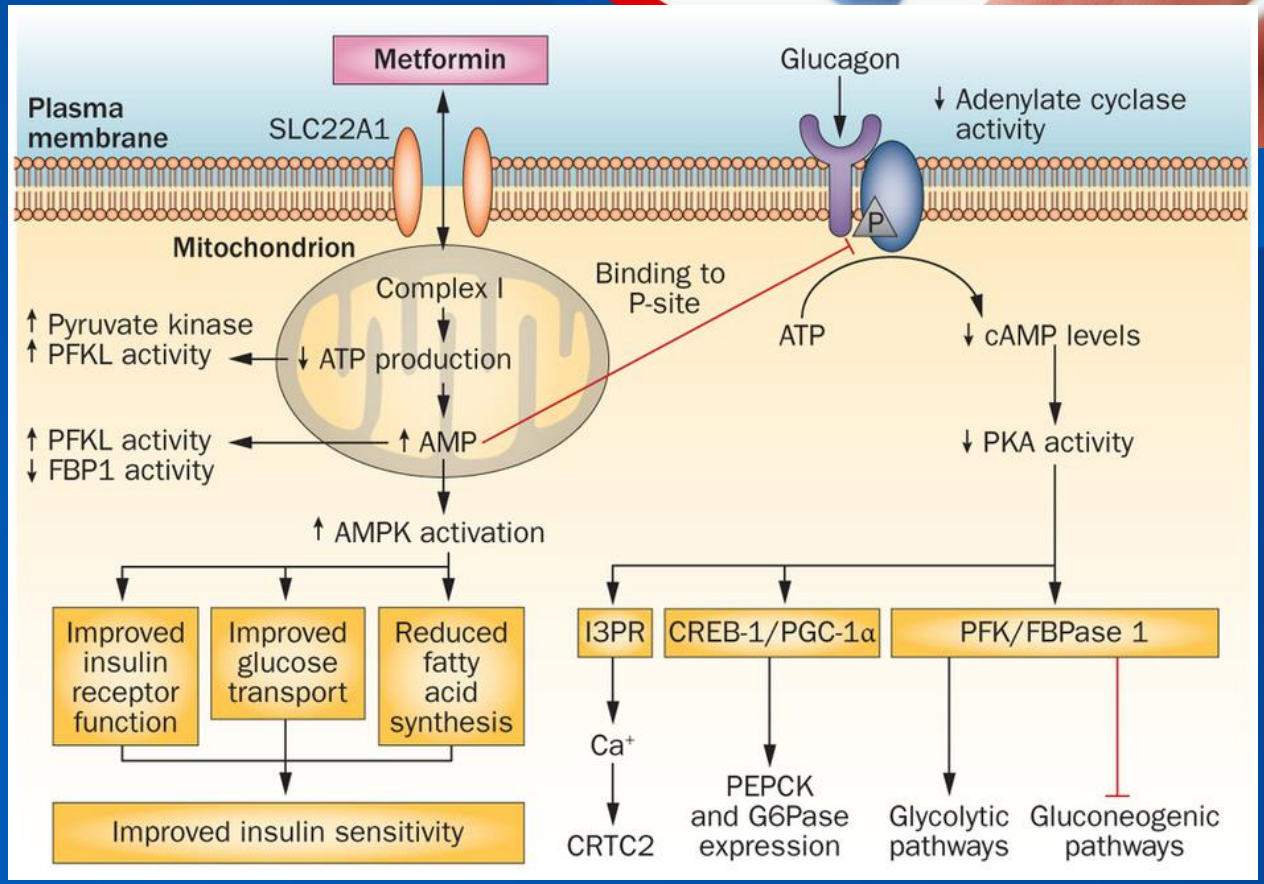
Metformin

- Typically initiated at diagnosis of T2DM; Most common first line agent
- Decreases hepatic glucose production; increase peripheral insulin sensitivity; can be used in patients without islet function
- No weight gain or hypoglycemia
- Risk of lactic acidosis (contraindication in renal impairment, avoid using with contrast)
- GI side effects common

Goat's rue –French lilac

Metformin

- Major mechanism of action: decrease mitochondrial ATP production
  - Increases expression or activity of glycolytic enzymes and GLUT-4, decreases activity of gluconeogenic enzymes
  - Net: ↓hepatic glucose production and ↑ glucose uptake in muscle and adipose.
- Can reduce plasma glucose levels by 25% and decrease hemoglobin A_{1c} by 1-2%. Also lowers plasma triglyceride levels, weight loss
- Does not lead to hypoglycemia when used alone


Metformin
Glucagon
Plasma membrane
SLC22A1
↓ Adenylate cyclase activity
P
Mitochondrion
Complex I
Binding to P-site
↑ Pyruvate kinase
↑ PFKL activity
↓ ATP production
ATP
↓ cAMP levels
↑ PFKL activity
↓ FBP1 activity
↑ AMP
↓ PKA activity
↑ AMPK activation
Improved insulin receptor function
Improved glucose transport
Reduced fatty acid synthesis
I3PR
CREB-1/PGC-1α
PFK/FBPase 1
Ca+
PEPCK and G6Pase expression
Glycolytic pathways
Gluconeogenic pathways
CRTC2
Improved insulin sensitivity

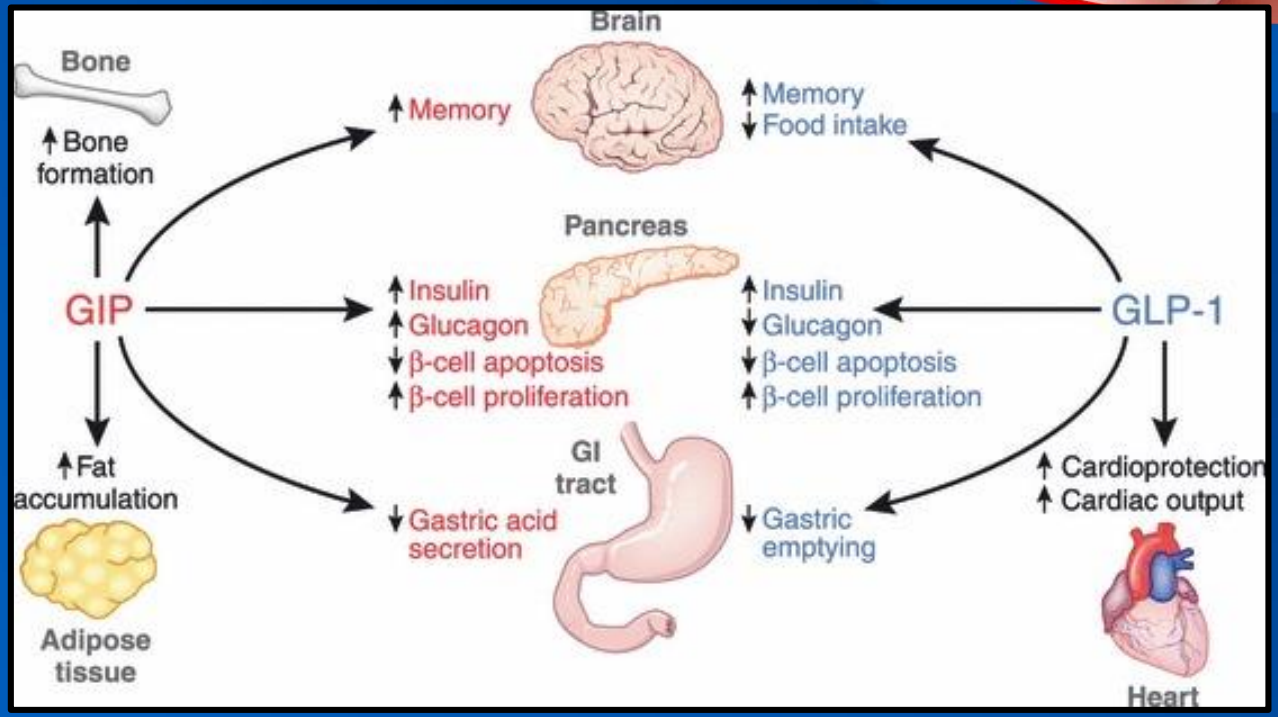
Treatment of T2 DM

- Lifestyle modifications
- Metformin
- Incretin/injectables or other oral meds
- More oral meds
- Insulin

Incretins

- Gut hormones that stimulate insulin secretion
  - Glucagon-Like Peptide-1 (GLP-1)
  - Glucose-dependent Insulinotropic Polypeptide (GIP)

Incretin effects



GLP-1 Receptor Agonists

- Glucagon-like peptide (GLP-1)
- Secreted from the intestine on ingestion of glucose; stimulates insulin secretion from pancreatic β cells (an “incretin”)
- Binds to a receptor (GLP-1receptor)
- GLP-1 mimics (agonists)
- Injectables – 2x Day; Newer versions – 1x/week
- 1 oral
- Cardioprotective
- Many other beneficial effects: decrease appetite, decreased glucagon secretion, weight loss
- Potential side effects: Thyroid C-cell hyperplasia/cancer , N/V, pancreatitis


Byetta
10


VICTOZA
liraglutide
(rDNA origin) injection


trulicity
(dulaglutide)
injection
1.5 mg/0.5 mL
trulicity
(dulaglutide)
injection
0.75 mg/0.5 mL

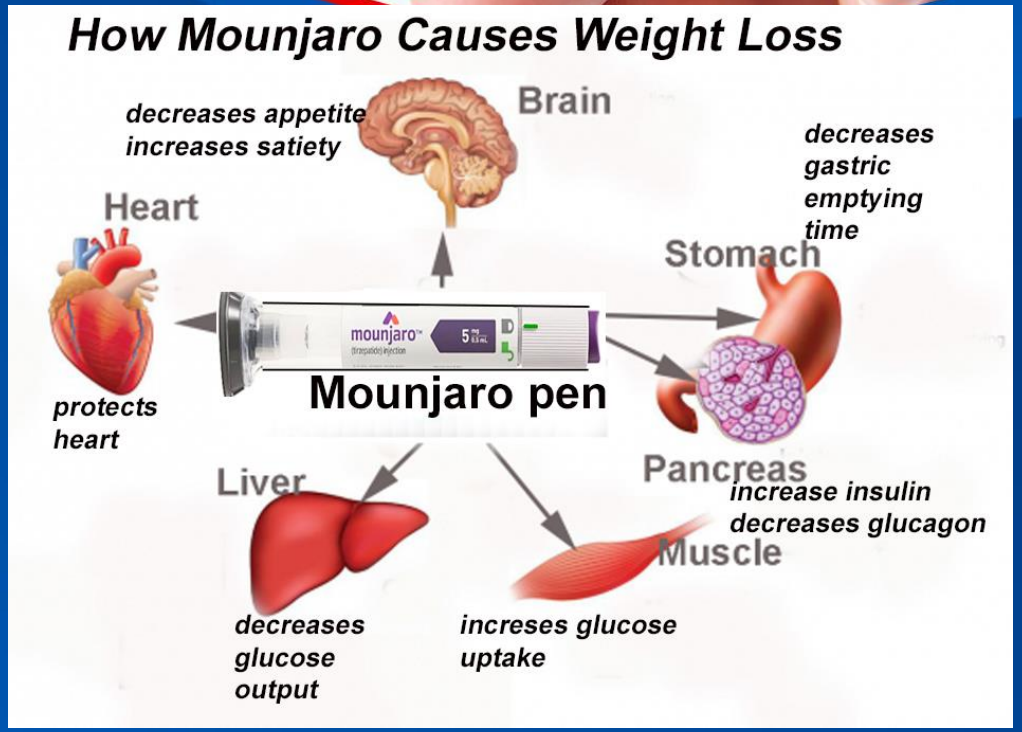

OZEMPIC
(semaglutide) injection
For Single Patient Use Only
OZEMPIC
(semaglutide) injection
For Single Patient Use Only

G1P

- Not as successful a drug as GLP-1; dual effect increases glucagon and insulin release. Glucagon decreases insulin
- HOWEVER

NEW!!! Dual GIP GLP1 receptor agonist drug

- Mounjaro (Tirzepatide) injectable once a week
- Treatment of obesity
- Treatment of Diabetes - FDA approved May 2022
- Multiple clinical trials – more weight loss than GLP1 receptor agonist alone; lowered HgA1C to 7%



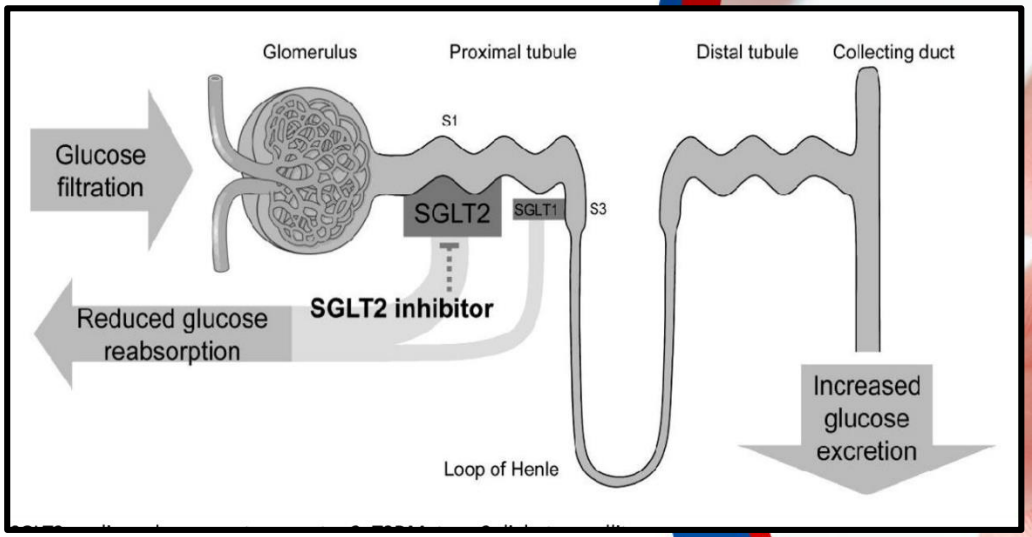
Sodium Glucose co-transporter (SGLT2) inhibitors (PO)

Jardiance

Mechanism

Inhibits the sodium glucose co-transporter 2 in the kidney→ ↑ urine glucose → ↓ blood glucose

Lowers the threshold for glucose excretion by the kidney



SGL2 inhibitors

- Benefits:
  - Decreases A1c by 0.5-1%
  - Weight loss of 2-8%

Proven to be cardioprotective for heart failure and atherosclerotic disease

- Side effects:

  UTI
  Vulvovaginal candidiasis (common)
  Ketoacidosis (rare)

- Caution:

  Renal insufficiency (GFR < 40 mL/min)
  Hypotension
  hyperkalemia

DPP-4 Inhibitors
“gliptins”

- Incretin (GLP-1) is rapidly broken down by dipeptidyl peptidase-4 enzyme (DPP-4)
- Increases GLP-1 by inhibiting the enzyme that breaks it down (so increases glucose dependent insulin release)
- Used alone or in combination
- Does not produce satiety or delay gastric emptying

Considerations in the selection of antihyperglycemic therapy

- Efficacy
- Hypoglycemia
- Weight Change
- CV effects
  - ASCVD
  - CHF
- Cost
- Oral vs SQ
- Renal effects
  - Progression of CKD
  - Dosing Considerations
- Additional Considerations

Thiazolidinediones: Pioglitazone

- Activate nuclear receptors: peroxisome proliferator-activator receptors (PPAR-γ).
- Adipose tissue – stimulate fat synthesis and inhibit lipolysis - leads to decrease in FFA and increase insulin sensitivity
- Increases gene expression in muscle, liver and fat to increase insulin sensitivity
- Seem to have additional beneficial effects on blood vessels to reduce hypertension and atherosclerosis
- Can be used as monotherapy or in combination with metformin or sulfonylureas
- Can worsen heart failure
- Weight gain

Sulfonylureas

- Bind to and inhibit ATP-sensitive K+ channels causing K+ to stay in the cell causing membrane depolarization, opening Ca channels which stimulates insulin release
- Oral
- Cause hypoglycemia and weight gain

Side effects of Diabetes drugs

HYPOGLYCEMIA

- YES
  - Insulin
  - Sulfonylureas
- NO
  - Metformin
  - GLP-1 RA
  - TZD

WEIGHT CHANGE

- GAIN
  - Insulin
  - Sulfonyureas
- LOSS
  - GLP-1
  - SGL2
  - Metformin (modest)
- NEUTRAL
  - DPP4 Inhibitors

Drugs that offer cardioprotection

Atherosclerotic CV disease

- BENEFIT
  - SGLT2 i
  - GLP-1
- POTENTIAL benefit
  - Metformin
  - some TZD
- NEUTRAL
  - DPP 4 in
  - Insulin
  - Newer sulfonylureas
- RISK
  - Some SULFONLYLUREAS

CHF

- BENEFIT
  - SGLT2i
- NEUTRAL
  - Metformin
  - GLP-1
  - Insulin
  - Sulfonylureas
- RISK/Potential risk
  - TZD
  - DPP 4 i

Obesity management
Bariatric Surgery

- Obesity management can delay progression from Prediabetes to T2DM.
- Moderate weight loss improves glycemic control and reduces the need for medication
- If have BMI of ≥35 and have not been able to achieve target fasting blood sugar
- Metabolic surgery – improves glycemic control, leads to weight loss, improved QOL, improved CV outcomes, and may even lead to remission of T2DM.
- Can resolve diabetes even before the weight loss
- Long term medical support and monitoring of micronutrient, nutritional, and metabolic status is necessary
- Hypoglycemia –Management includes education, nutrition therapy, & experienced dietician. CGM should be considered to improve safety NEW

Body Mass Index

- https://www.cdc.gov/widgets/healthyliving/index.ht micalculator **Adult Body Mass Index Calculator Widget**

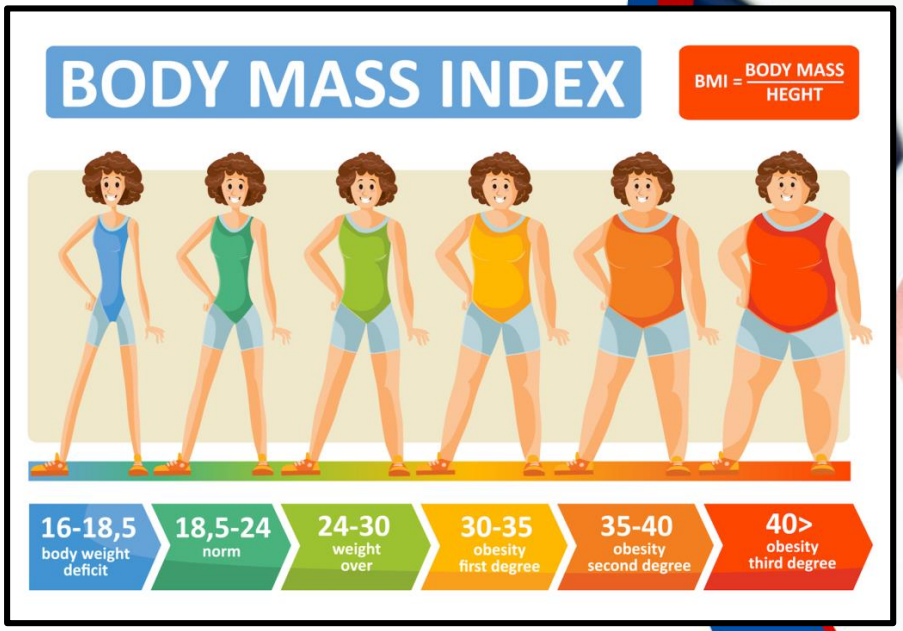
Adult and Child BMI Calculator

Calculate BMI for: Adult Age 20+

Weight: pounds

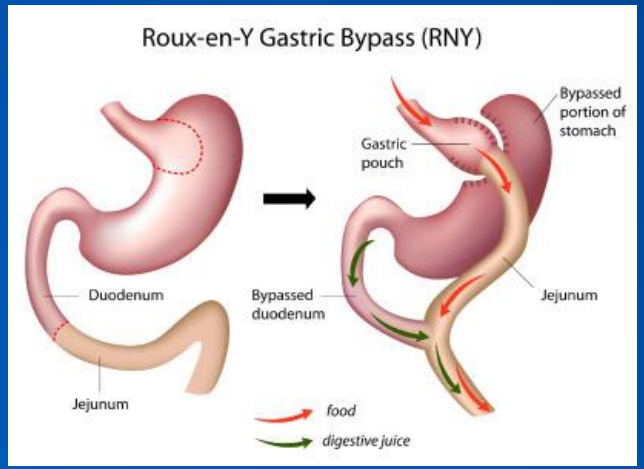
Height: inches

BMI	Status
≤ 18.4	Underweight
18.5 - 24.9	Normal
25.0 - 39.9	Overweight
≥ 40.0	Obese



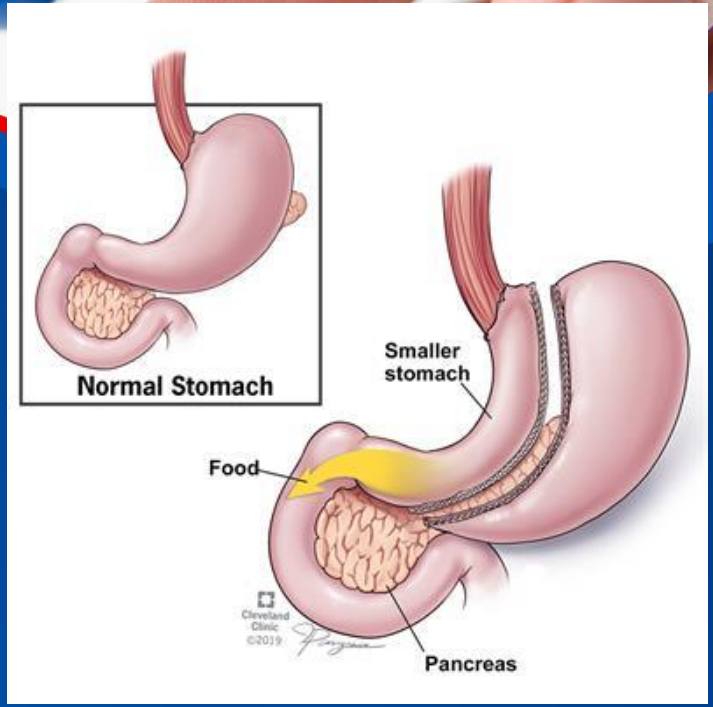
Gastric bypass
Roux-en-Y procedure

- **Restriction:** The surgeon separates the upper portion of the stomach from the lower portion. The upper portion (or the "pouch") is then connected to a limb of the small intestine, called the "Rouxlimb." The new stomach pouch restricts the amount of food you can eat, making you feel full after eating only a small amount of food.
- **Malabsorption:** Once the smaller pouch is created, the surgeon reroutes your digestive system to bypass the larger part of your stomach and part of your small intestine. The result of the bypass is you absorb fewer calories and nutrients from the food you eat (malabsorption).



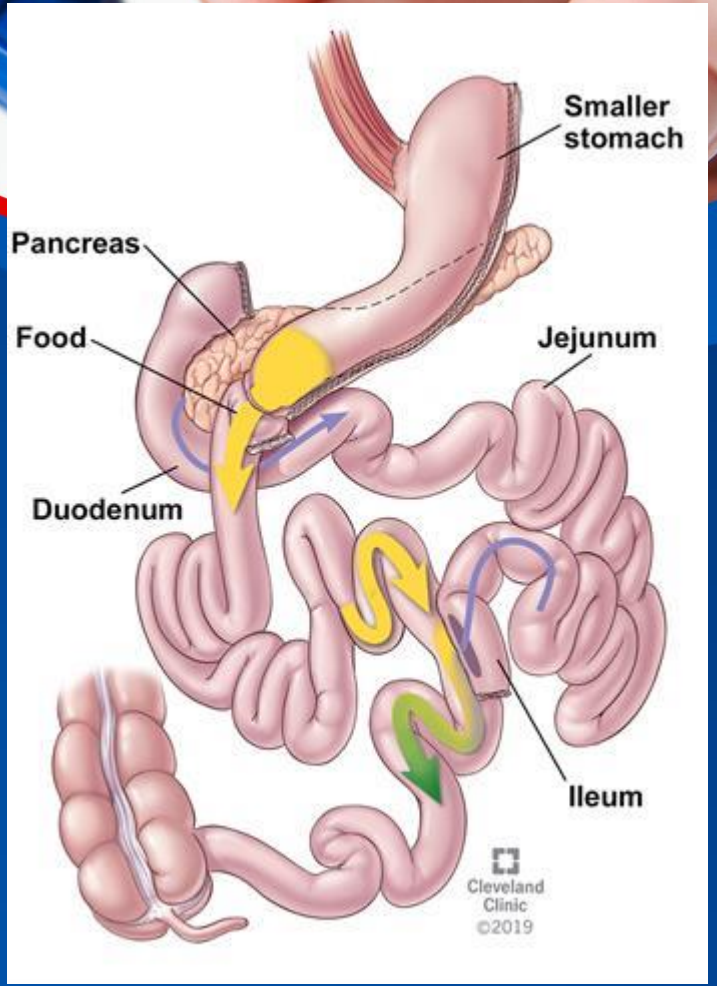
Sleeve gastrectomy

- reduces the size of the stomach and limits food intake
- Easier to perform than gastric bypass



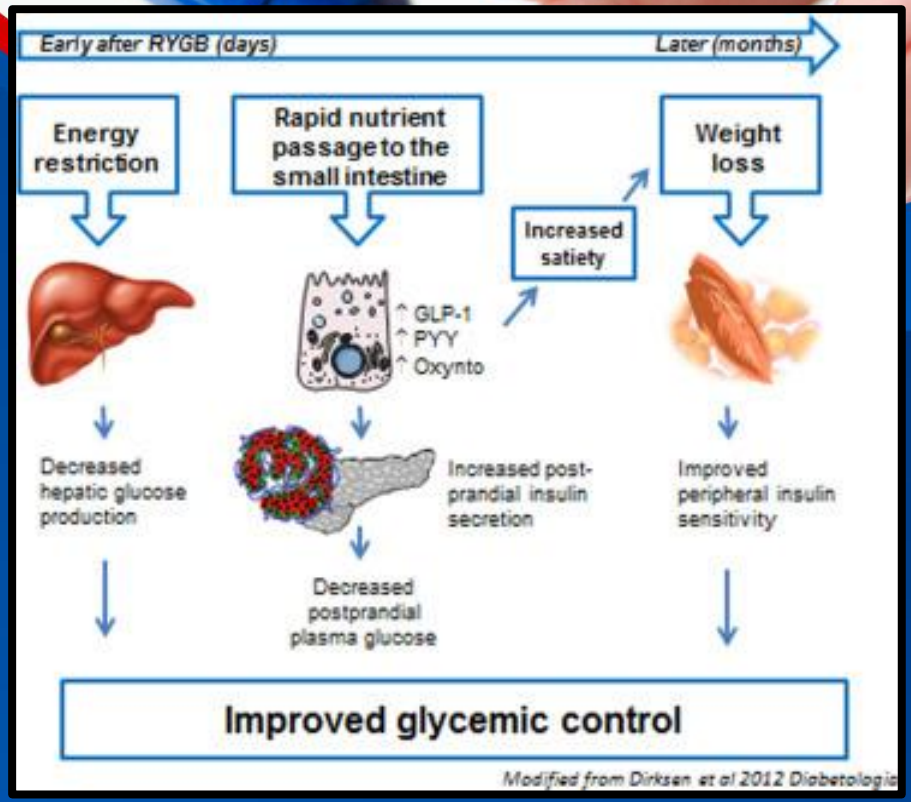
Duodenal switch
BMI > 50

- Large bypass procedure
- Duodenum, jejunum and part of the proximal ileum are bypassed and then connected to a point near the ileocecal valve.



Effects on Diabetes

- Hepatic insulin resistance in improved (50%)
- GLP-1 is increased
- Decreased after meal blood glucose
- Weight loss – improves peripheral insulin sensitivity



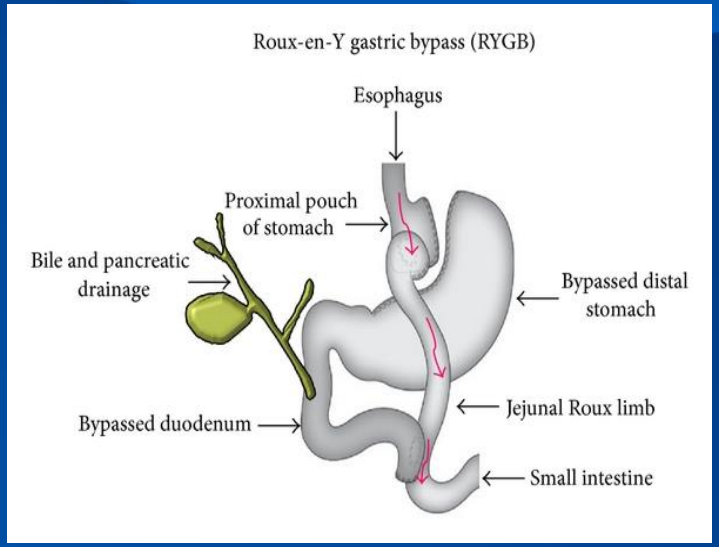
Risks and Side effects of Bariatric Surgery

- Poor response to anesthesia
- Damage to nearby organs during surgery
- Bleeding
- Blood clot formation
- Infection

- Peritonitis, or inflammation in the peritoneum, the tissue that covers and supports the organs in the abdomen
- Blockages in the intestine
- Development of gallstones and kidney stones
- Narrowing of the connection between the stomach and the intestine, also called anastomotic stenosis.
- Dumping syndrome (early and late): nausea, stomach pain and vomiting after eating.
- Malnutrition

Vitamins and minerals

- Absorption of the majority of the nutrients takes places in the jejunum, with a few exceptions: iron is absorbed in the duodenum, and vitamin B12 and bile salts are absorbed in the terminal ileum.
- During gastric bypass, the duodenum is entirely bypassed, as well as the distal stomach and proximal jejunum, contributing to potential vitamin and mineral deficiencies.
- The most common deficiencies caused by Roux en Y gastric bypass malabsorption are that of iron, vitamin B12, folate, calcium and vitamin D.

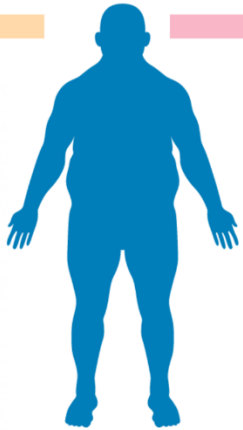


Diet

↓ PYY 3-36	↑ Ghrelin
↓ GLP-1	↓ Leptin
↔ Bile acids	↑ Gut microbiota (with weight loss)
↓ Perceived satiety	↑ Perceived hunger
↔ Food aversion	

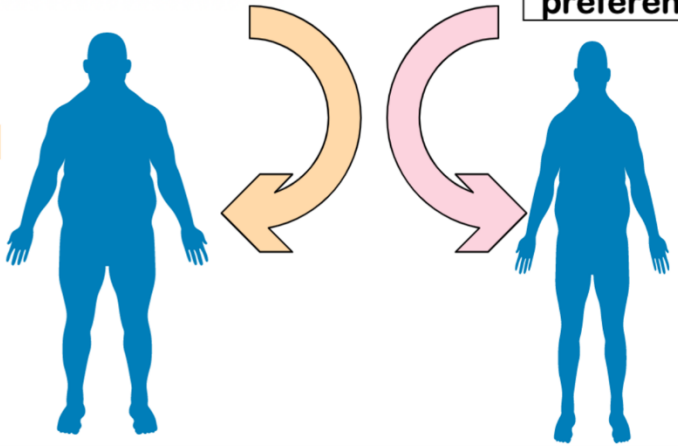
Bariatric Surgery

↓ PYY 3-36	↓ Ghrelin
↑ GLP-1	↓ Leptin
↑ Bile acids	↑ Gut microbiota (leaner)
↑ Perceived satiety	↓ Perceived hunger
Altered food preferences	



To defend a greater body weight, homeostatic mechanisms would be used

In 5 years average 80% weight will be regained



18% average weight loss 20 years after RYGB

Reset "set point" of the bodyweight to a lower weight

Metabolic alterations seen in Diet vs. Bariatric Surgery

End

- Questions?
- gathas@lsuhsc.edu