SESSION 3
PEDIATRIC SESSION

INSULIN RESISTANCE AND WEIGHT

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CONFLICTS OF INTEREST

I have no conflicts of interest related to this presentation

OUTLINE

- Review the different types of diabetes
- How and why insulin resistance affects your body and blood sugars
- Review reasons for insulin resistance
- Discuss consequences of insulin resistance
- Review methods to treat insulin resistance
    - Lifestyle changes
    - GLP1 Agonists
    - Others

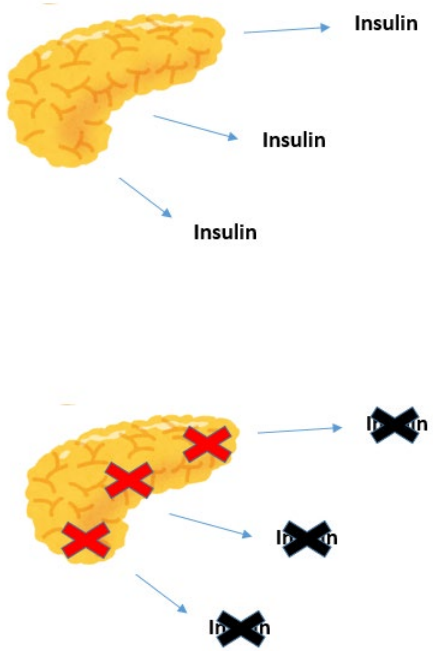
INSULIN: A BRIEF REFRESHER

- An important hormone made by the beta cells of the pancreas
- Insulin allows blood sugar to enter the body's cells and be used as energy
- Helps also build proteins and other parts of the body
- Extra blood sugar is then stored as adipose (fat) cells, which the body can use as energy later
- Without enough insulin, high blood sugars (hyperglycemia and diabetes can occur)

DIFFERENTIATING DIABETES

TYPE 1 DIABETES

- **Insulin Deficiency**
- Destruction of insulin producing cells of the pancreas by body's own antibodies
- Leads to an overall lack of insulin
- Body is unable to maintain normal blood sugars and prevent formation of an acid (ketones) in the body
- Treatment is insulin



TYPE 2 DIABETES

- **Insulin Resistance**
- Body does not react as much to its own insulin, leading to higher blood sugars
- If blood sugars not controlled, pancreas can eventually "burn out" and stop producing enough insulin
- Treatments include lifestyle changes, oral medications, GLP1 injections, and insulin

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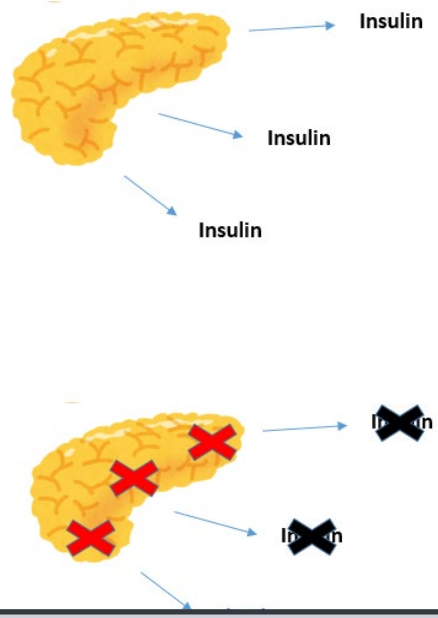

"Double Diabetes" or Type 1.5 Diabetes

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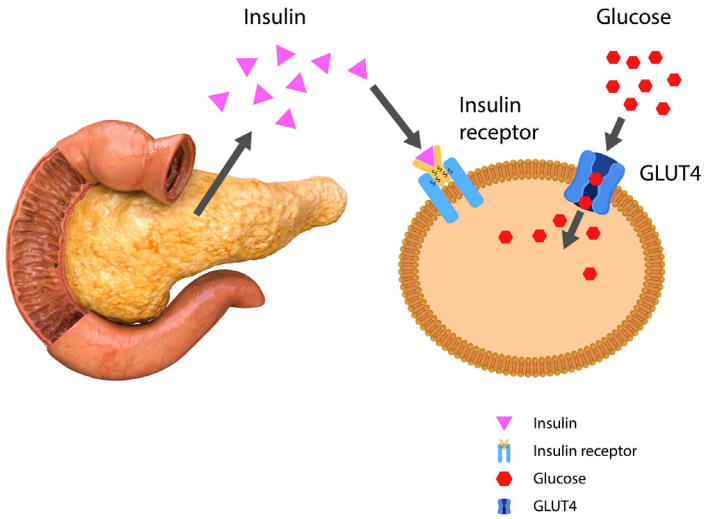
INSULIN RESISTANCE: WHAT IS IT?

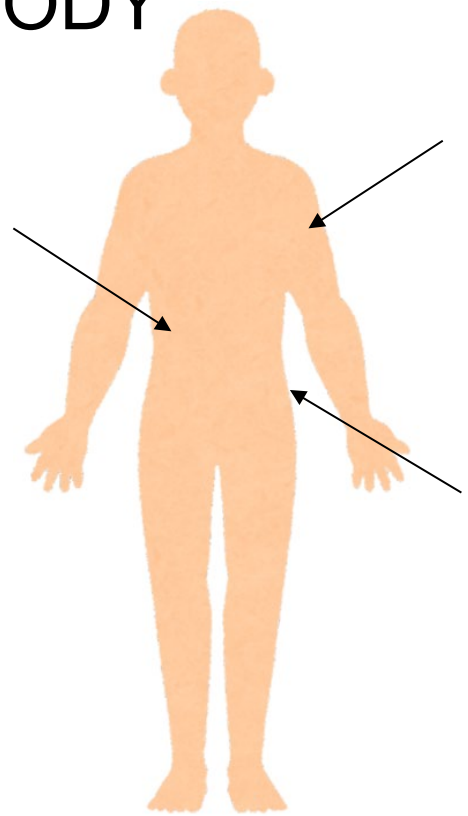
- Insulin does not have as much of an effect on the body
- Can happen with insulins made by the person's own body or to what is given through a pump or shot
- If the body stops reacting as strongly to the insulin:
  - Not as much glucose enters the cell
  - Glucose can build up in the blood stream
  - Ketones can begin to form when they should not, leading to acidosis
- The amount of insulin the body sees has to be increased



Normal Process

HOW INSULIN RESISTANCE IMPACTS THE BODY

- Main areas of resistance:
  1. Skeletal muscles
  2. Liver
  3. Adipose (fat) tissue
- Resistance eventually leads to:
  1. Higher sugars since the liver is not suppressed from making more glucose
  2. More free fatty acids, increasing the resistance
  3. Increased fat storage
     - Intra-abdominal (“central obesity”)
     - In muscles
     - Liver
     - Blood vessels



CAUSES OF INSULIN RESISTANCE

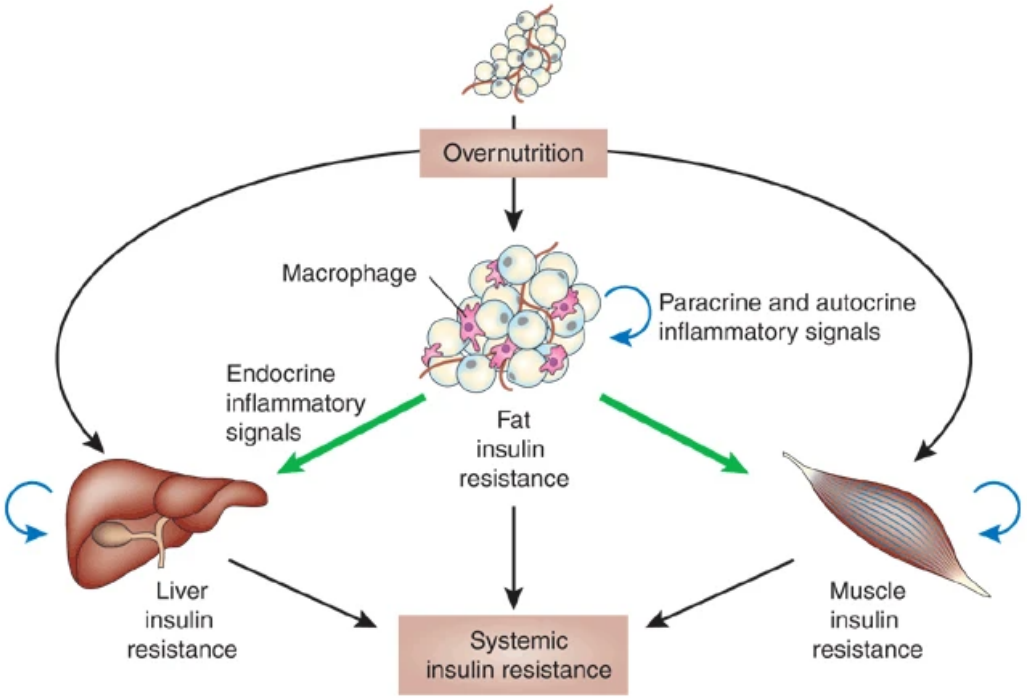
1. Puberty*
2. Obesity*
3. Pregnancy
4. Lipodystrophy
5. Stress
6. Medications (steroids, certain depression/anxiety medications)
7. Other rarer causes

PUBERTY AND INSULIN RESISTANCE

- Time of significant change in a person's life, including their resistance to insulin
- Relative insulin resistance of puberty first noticed in the 1980s
- Reasons:
  - Large number of hormonal changes during this time
    - Growth hormone, particularly in the very early morning hours
    - Sex steroids (estrogen and testosterone) and androgens
  - Changes in body composition, particularly fat mass
  - Changes in cholesterol levels
- Sensitivity generally returns to normal following the end of puberty
- Obese youth are more insulin resistant going into puberty and sensitivity does not always recover at the end

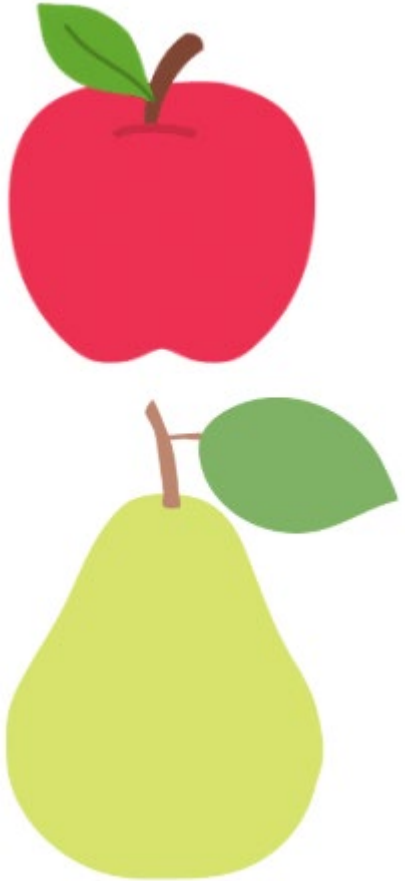
OBESITY AND INSULIN RESISTANCE

- Higher amounts of central obesity lead to extra resistance:
  - Inflammation:
    - Cytokines from macrophages
    - Inflammatory proteins
  - Overproduction of some hormones that work against insulin
  - More free fatty acid production from lipolysis
- Can be difficult to navigate as insulin itself can lead to weight gain



METABOLIC SYNDROME

- Otherwise known as: Syndrome X, insulin resistance syndrome, obesity dyslipidemia syndrome
- Diagnostic criteria has changed over the years
    - At least 3:
        - Abdominal obesity
        - High serum triglycerides
        - Low HDL cholesterol (“good cholesterol”)
        - High blood pressure
        - High fasting blood sugars
- More common in adults but occurring more frequently in children and teens

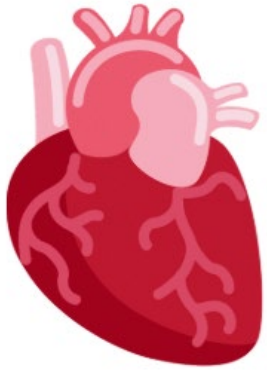


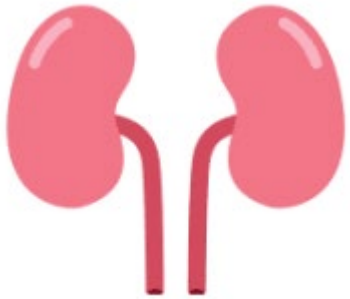
DOUBLE DIABETES OR INSULIN RESISTANCE IN T1D

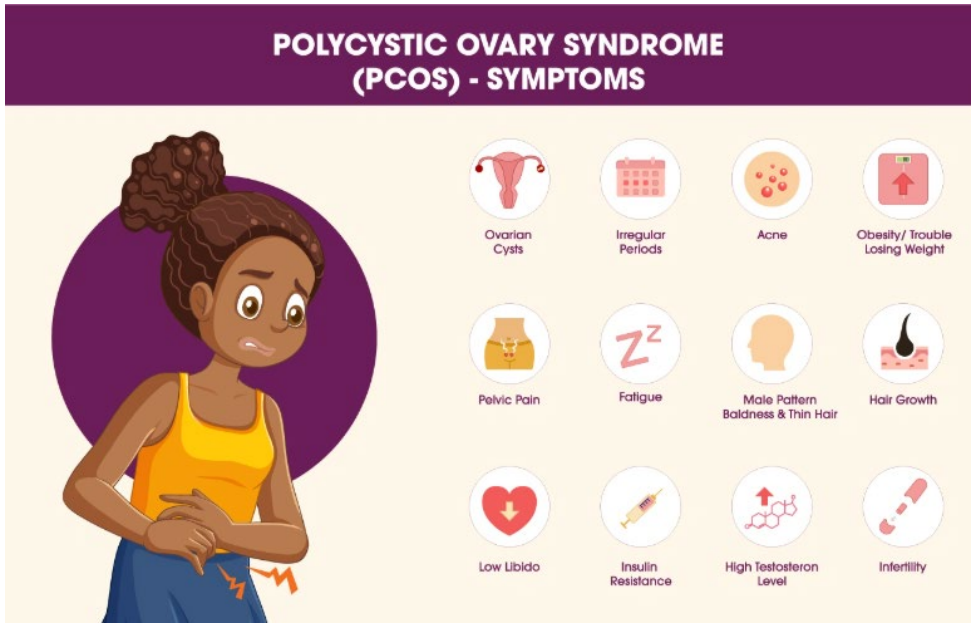
- Can be much more difficult to make the diagnosis of metabolic syndrome in these individuals
- Possible factors leading to increased IR:
  - Family history of T2D
  - Weight gain from insulin therapy
  - Maladaptive eating pattern, especially around lows
  - Chronic hyperglycemia leading o glucotoxicity
  - Insulin therapy itself
    - Peripheral hyperinsulinemia and hepatic hypoinsulinemia
    - Changes in expression of the insulin receptors in peripheral tissues
- Presence of IR still associated with worse long term outcomes

CONSEQUENCES OF INSULIN RESISTANCE

- Worsening glycemic outcomes and complications
- Cardiovascular disease
- Kidney disease
- Skin findings
- Polycystic ovary syndrome (PCOS)
- Liver disease
- Obesity-related cancers (endometrial cancer)







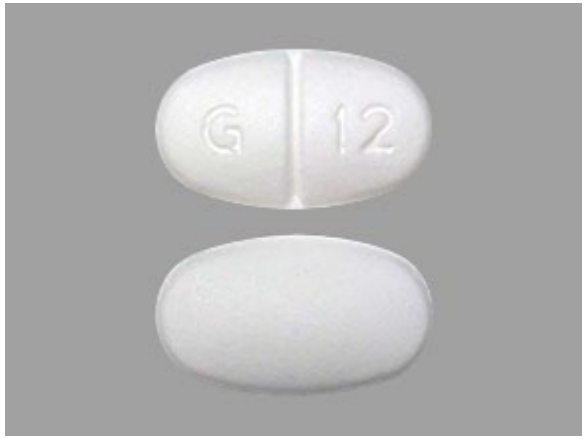
TREATMENT OF INSULIN RESISTANCE

LIFESTYLE CHANGES

- Primary goal is weight reduction
  - Even losing 5-10% of body weight can make a huge difference in insulin sensitivity
- Dietary changes
  - Unclear the best for weight loss (Mediterranean, DASH, etc)
  - Generally balanced diet (high protein, low fat) and limited processed food
- Physical Activity
  - Combination of aerobic and resistance trainings, totaling 150 minutes per week
  - Improves blood sugars in general
    - Muscles can use glucose in a way separate from insulin
    - Improved insulin liver sensitivity
  - Works best alongside dietary changes
  - Helps improve other parts of person's health (blood pressure, cholesterol levels)

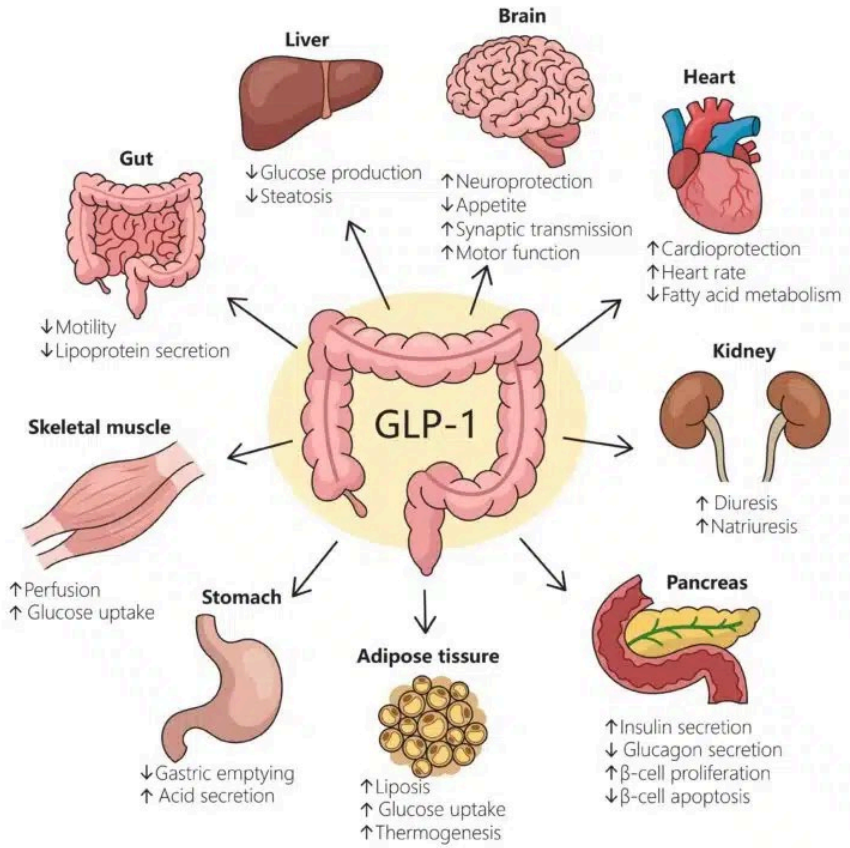
METFORMIN

- Oral medication used to treat type 2 diabetes, pre-diabetes, PCOS, and obesity
- Mechanisms:
  - Stops the liver from making its own glucose
  - Increase glucose uptake by insulin in peripheral tissues through a different pathway
- In Type 1 Diabetes:
  - Research showed some weight reduction and decreased in total daily dose
  - Not sustained in the long-term and no improvement in glycemic control
  - Possible use to manage cardiovascular risk or improve sensitivity for those with IR



GLUCAGON-LIKE PEPTIDE 1 (GLP1)

- Important hormone made by the small intestine and colon
- Impacts multiple areas of the body to help regulate blood sugars
- Serves 3 main functions:
  1. Stimulates your pancreas to release more insulin in response to a meal
  2. Slows down your gut to stop the blood sugar from rising as quickly
  3. Acts on the brain to reduce your appetite
- Naturally made GLP1 lasts only for minutes



GLP1 AGONISTS

- Synthetic form of the naturally made GLP1
- Indicated to treat type 2 diabetes and to help with weight loss
- Daily:
  - Liraglutide (Victoza, Saxenda)
- Weekly:
  - Tirzepatide (Mounjaro, Zepbound
  - Semaglutide (Ozempic, Wegovy)
  - Dulaglutide (Trulicity)
  - Exenatide ER (Bydureon)
- Doses are started low and slowly increased over the next few weeks to months to the highest tolerated dose
- Often significant improvements in hemoglobin A1c and weight reduction

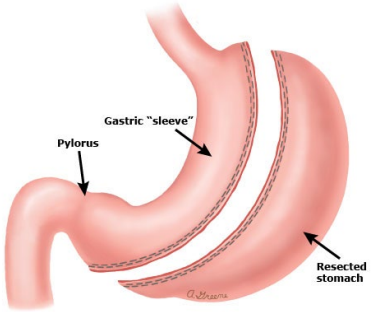
GLP1 AGONISTS: SIDE EFFECTS

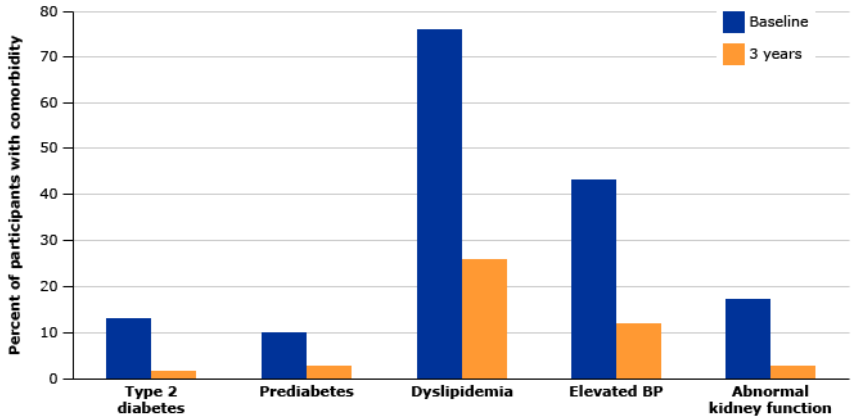
- Gastrointestinal: Nausea, vomiting, diarrhea
  - Occur quite frequently
  - Attempt some dietary changes (smaller, less fatty meals, increased water intake)
  - Can be significant and can lead to discontinuation by patients
  - Can be difficult to navigate for someone with type 1 diabetes due to ketone development
- Pancreatitis
- Hypersensitivity/allergic reactions

- Weight loss often not maintained once medication is stopped

OTHER OPTIONS

- Bariatric Surgery
  - Similar outcomes and weight reduction to GLP1
  - Sleeve gastrectomy (most common in adolescents)
  - Roux-en-Y gastric bypass (higher risk of nutritional deficiencies)
  - Long-term weight loss but generally immediate improvement in glucoses
- Other medications for weight loss (Phentermine, Topiramate):
  - More complicated to navigate around diabetes, especially type 1
- Type 2 Diabetes medications (SGLT2 inhibitors):
  - Not approved for people with T1D but may be promising
  - Decreases glucoses by causing kidneys to pee out more
  - Improves heart and kidney outcomes for those with T2D
  - Increased risk of DKA for those with T1D





CONCLUSIONS

- Insulin resistance is increasingly common, including in those with type 1 diabetes
- Insulin resistance can lead to higher insulin requirements, higher blood sugars, and more long term health consequences
- Multiple factors can lead to insulin resistance, with obesity being a primary driver
- Main treatment is lifestyle changes
- Some promise for medications like GLP1, though therapy is likely life-long