Understanding CFRD

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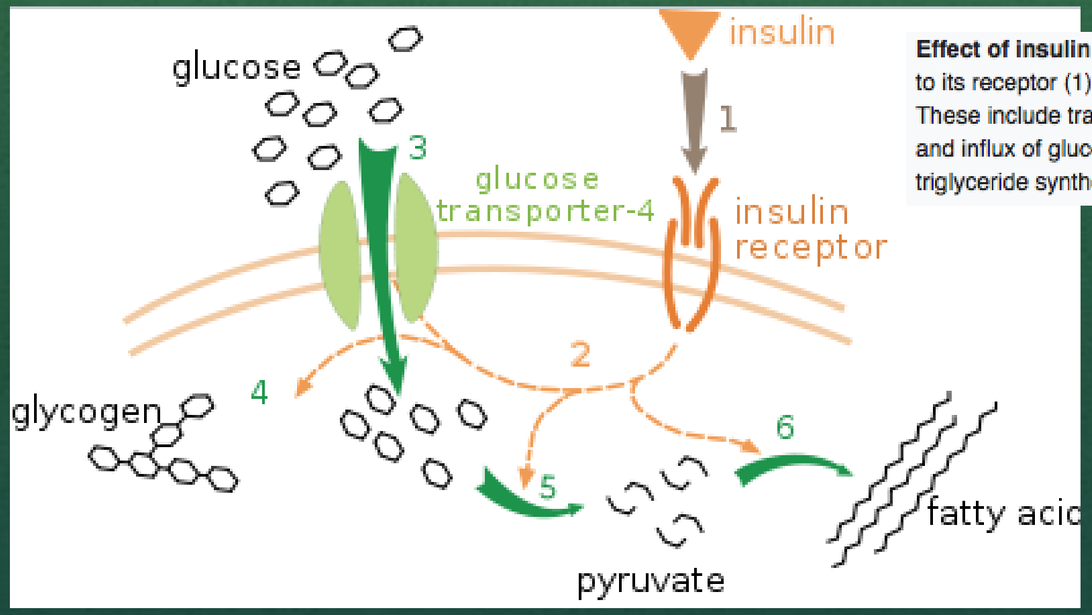
Why does a Pediatric Endocrinologist come to CF clinic?

- Blood Sugars
- Growth

Cystic Fibrosis Related Diabetes (CFRD)

- Different from either type 1 or type 2 diabetes
- Type 1: Insulin deficiency
- Type 2: Insulin resistance

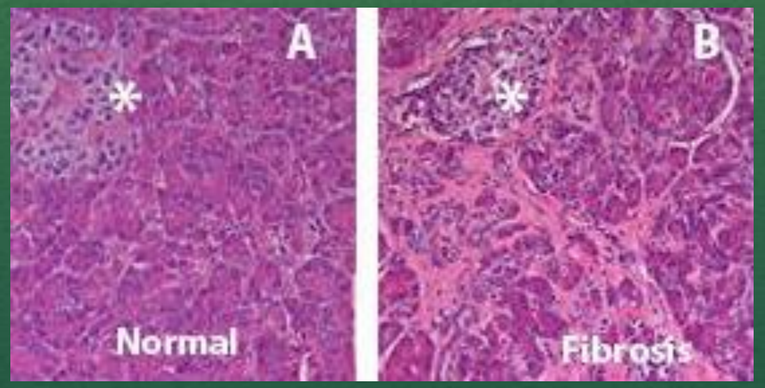


Effect of insulin on glucose uptake and metabolism. Insulin binds to its receptor (1), which starts many protein activation cascades (2). These include translocation of Glut-4 transporter to the plasma membrane and influx of glucose (3), glycogen synthesis (4), glycolysis (5) and triglyceride synthesis (6).

Believe it or not, the best diagram I could find to demonstrate insulin's mechanism of action came from Wikipedia!

CRFD shares features of both T1 and T2 DM

- Relative insulin deficiency from destruction of islet cells of the pancreas



From Pancreas.org. The asterisk shows the islet cells, or the endocrine tissue where insulin is produced

CRFD shares features of both T1 and T2 DM

- Insulin resistance is associated with acute exacerbations or chronic progression of pulmonary disease
- Family history of type 2 diabetes increases risk of CFRD 3x

Prevalence of CFRD

- From MN
  - 2% under age 10
  - 19% age 11-17
  - 40% age 18-29
  - 45-50% over age 30
- From Germany/Austria
  - 11% <20 years old
  - 25% at 35 years of age

Awareness has been increasing

- Australian Review in 2008 showed 10x more people diagnosed with CFRD in 2008 compared to 2000
  - Better screening practices
  - Longer life spans

Risk factors for CFRD

- Pancreatic Insufficiency
- Delta-F508 genotype
- Age
- Female gender
- Poor lung function; impaired nutrition
  - Consequence or cause?
- Family history of T2DM gives 3x rate of CFRD

Stages of CFRD

- 1. Hyperglycemia in response to glycemic load
- 2. Fasting hyperglycemia

Consequences of CFRD

- Declining pulmonary function
  - Elevated glucose levels promote bacterial growth
  - Increased lactate acidifies the airway surface liquid
  - Decreased epithelial cell repair
  - Impairment of epithelial cell K channel function, which is important in mucus clearance

Consequences of CFRD

- Poor nutritional status
  - Insulin is an anabolic hormone
  - Hyperglycemia increases urine output and causes dehydration

Consequences of CFRD

- Microvascular Complications occur, but less than in T1DM
  - Retinopathy
  - Neuropathy
  - Nephropathy

- Macrovascular Complications are rare
  - Myocardial infarction
  - Atherosclerosis

Consequences of CFRD

- Mortality
  - Mortality rate is 3.5x greater in people with CFRD compared to people with CF, but not diabetes
  - Good news:
    - The mortality rate is dropping over time, from 6.7 deaths per 100 patient years to 3.5 deaths per 100 patient years from the 90's to 2008

Screening for CFRD

- The standard is an oral glucose tolerance test (OGTT)
- Fingerstick blood sugar at baseline; and then one and two hours after glucola
- Do it annually starting at age 10
- Screen fasting and postprandial sugars if hospitalized for exacerbation
- Screen with OGTT during pregnancy at end of first and second trimesters, and 6-12 weeks after delivery

OGTT results

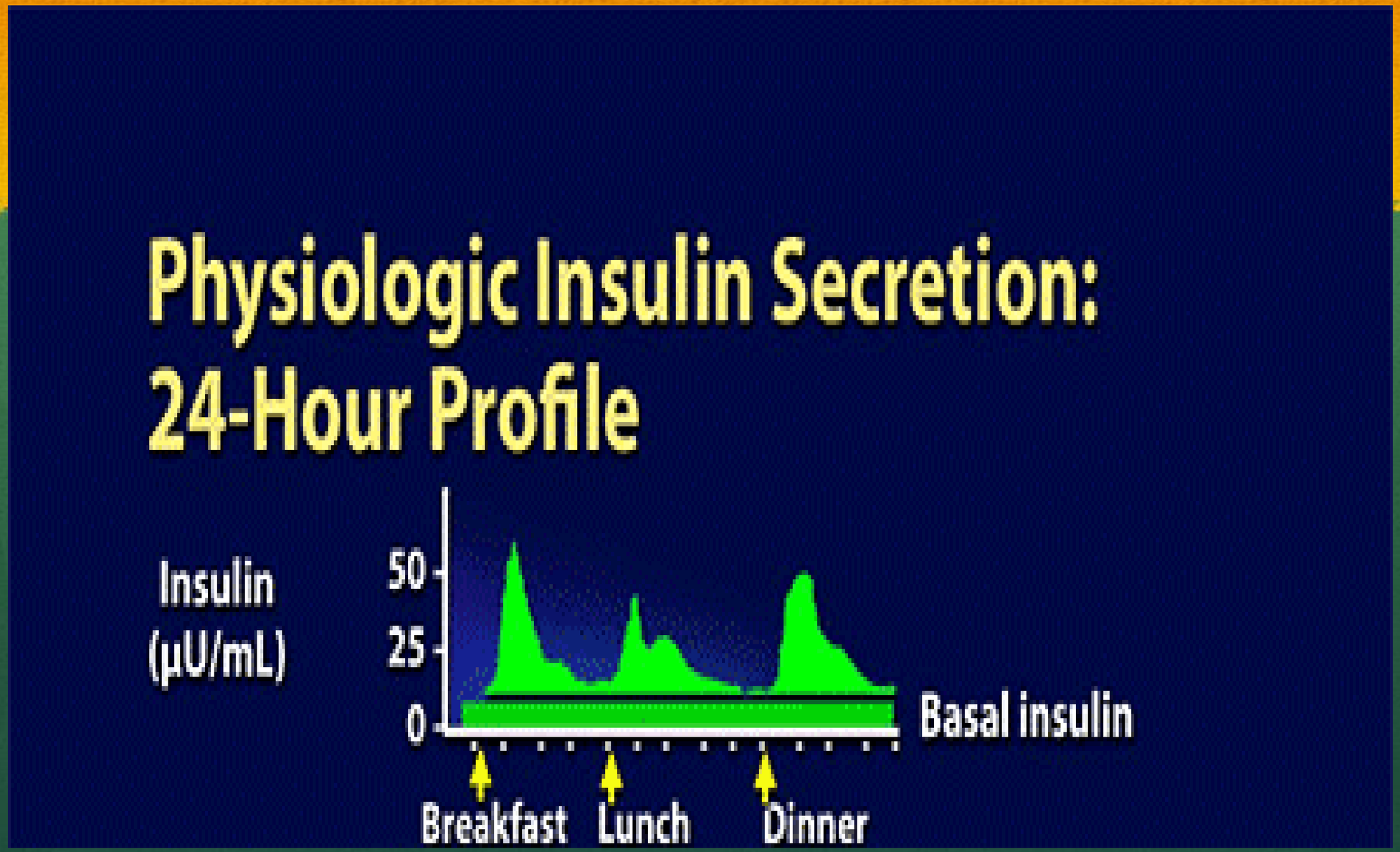
- Normal: fasting BG <100 and 2 hour <140
- Impaired fasting: fasting BG 100-125
- Indeterminate: 1 hour BG>200, but 2 hour <140
- Impaired glucose tolerance: 2 hour 140-200
- CFRD without fasting hyperglycemia: 2 hour>200 but fasting <126
- CFRD with fasting hyperglycemia: 2 hour>200 and fasting >126

Other screening methods

- Hemoglobin A1c – not very sensitive – only 16% of patients with CFRD have an A1c of >6.5% at time of diagnosis
- Clinical symptoms (frequent urination, thirst, weight loss) are also not always present when diagnosed with CFRD
- Home glucometry

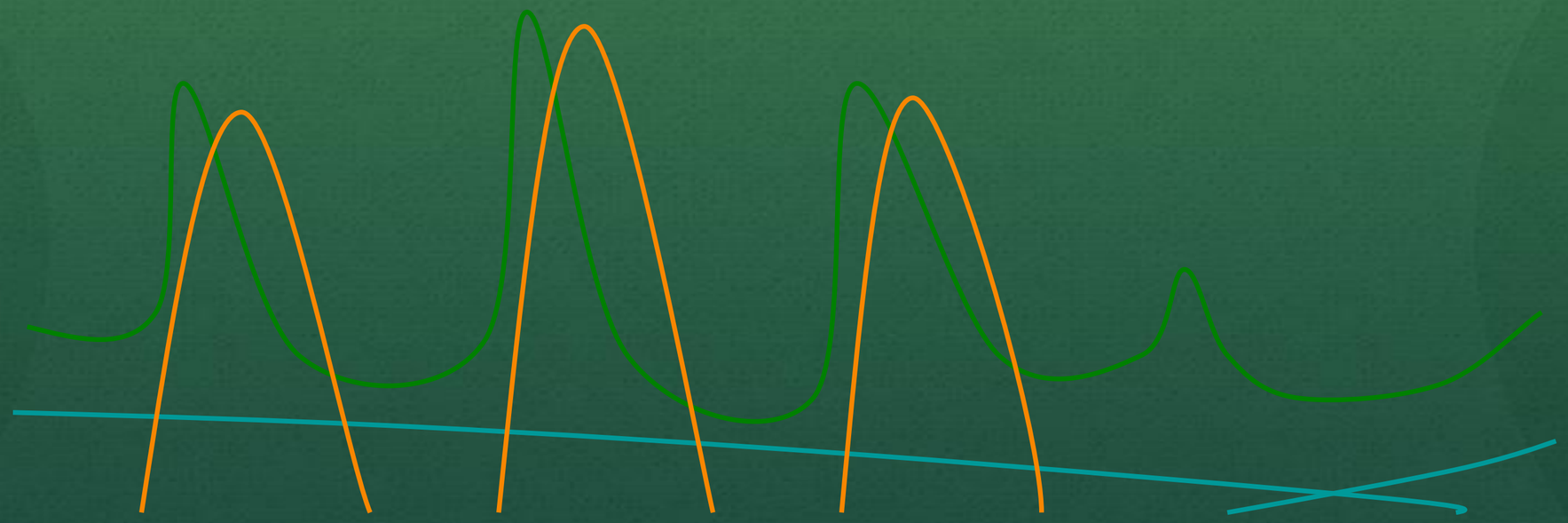
CFRD treatment

- Insulin
  - Basal
    - (Lantus, Levemir, Tresiba, Toujeo, Basaglar, Semglee)
  - Rapid Acting
    - (Humalog, Novolog, Admelog, Apidra, Fiasp, Lyumjev)
  - Intermediate Acting
    - NPH (very useful for overnight tube feeds)
  - Insulin pumps

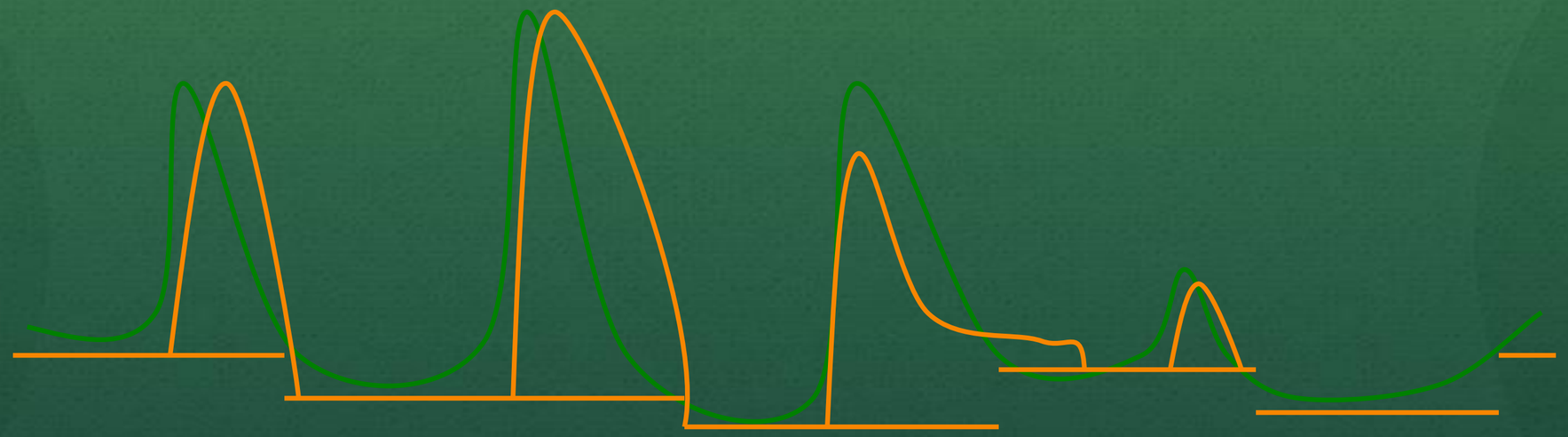


- From **Insulin-Treated Type 2 Diabetes: Balancing Physiologic and Individual Needs**
  Moderator: Richard S. Beaser, MD; Faculty: Martin J. Abrahamson, MD; Mark E. Molitch, MD

Comparison of Physiologic Insulin Secretion to a Basal/Bolus Regimen



Comparison of Physiologic Insulin Secretion to an Insulin Pump Regimen



Diet

- Most patients with CF benefit from foods to increase caloric intake, including carbohydrate-heavy beverages
- But in patients with CFRD, these carbohydrates can be counter-productive to weight gain
- Reduce the glycemic load, but maintain calories
  - Soft drinks, juice, and other sugar-containing beverages should be reduced

Monitoring

- Fingerstick blood sugar
  - Depending on degree of impaired glucose tolerance/diabetes, the frequency ranges from once a month to multiple times daily
- Continuous glucose monitoring
  - For those requiring frequent glucose checks, CGM's can be really useful

Oral Agents

- Previously the first line of treatment, pills have NOT been shown to have sustained benefit for treatment in Body Mass Index, Lung function or A1c

CFTR Modulators

- This class of drugs improves insulin secretion and glucose intolerance
- Kalydeco, Orkambi, Symdeko, Trikafta

Questions?

- Sources:
  - Moheet, Moran; “CF-related diabetes: Containing the metabolic miscreant of cystic fibrosis”; Pediatric Pulmonology. 2017; 52:S37-S43.
  - Donaghue, Robinson; “Cystic fibrosis-related diabetes mellitus”; UpToDate. 4/14/21

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