Recognizing & Treating Atypical Diabetes

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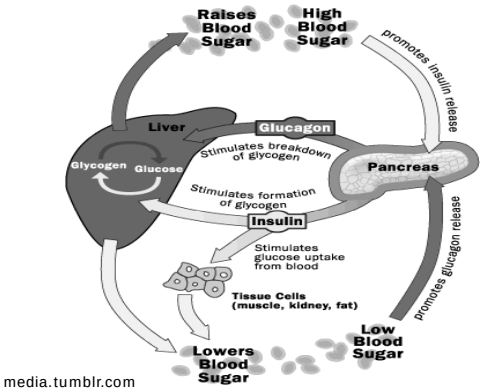
Objectives

- Recognize the major types of diabetes:
  - Type 2, Type 1A, Type 1B, MODY, LADA, Pancreatic diabetes, drug-induced DM
- Identify the laboratory tests used to differentiate between types of diabetes.
- Choose drug regimen modifications appropriate for drug-induced diabetes.
- Recognize appropriate drug therapy and monitoring regimens for atypical diabetes.

Glucose Homeostasis



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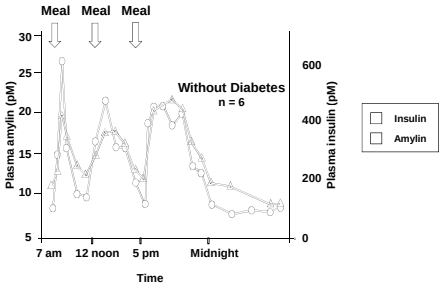
Insulin and Amylin Co-secreted



Koda et al, *Diabetes*. 1995; 44 (s1): 23BA.
Data on file. (Fineman)

Amylin

- Secreted by pancreatic beta-cells
- An anorectic hormone
- Works on the brain to stimulate the feeling of satiety.
- This results in decreased G.I. motility, slowed carbohydrate absorption, and decreased appetite.

Koda et al, *Diabetes*. 1995; 44 (s1): 23BA.

GLP-1

- "Incretin" hormone secreted by jejunal and ileal L cells in response to a meal
- Stimulates insulin secretion
- Decreases glucagon secretion
- Slows gastric emptying
- Reduces fuel intake (increases satiety)
- Improves insulin sensitivity

Diabetes Pathology

Type 1 Diabetes: Pathophysiology

- Typically autoimmune (~90%)
- Beta-cells destroyed by multiple antibodies.
- Impaired insulin secretion
  - Absolute insulin deficiency

T1DM

- Can occur at any age (but more in kids)
- Fast progression (the older the slower)
- Related to ketones @
  - Urine ketones
  - Ketoacidosis
    - Weight loss, N&V, lethargy

T2DM
Diagnosis characteristics

- Insidious
- Obesity (almost always), or weight gain
- Related to other IRS signs
  - Hyperlipidemia, acanthosis nigricans
- Older (↑Obesity = ↓Age; fatter = younger)
- Ethnic links
- Family history of T2DM
- No ketones (at diagnosis, typically)

Type 2 Diabetes: Pathophysiology

- Impaired insulin secretion
  - Absolute or relative insulin deficiency
- Impaired insulin action (sensitivity)
  - Insulin resistance

Atypical diabetes

Idiopathic type 1 diabetes

Type 1B Diabetes

- Also known as “Flatbush diabetes”
- African American and Asian men (18-25)
- Fluctuating insulin secretion
- No antibodies
- Many honeymoons

LADA

- Latent autoimmune diabetes of adulthood
- Like type 1 but diagnosed after age 25.
- ~20% of those with diagnosis of T2 may actually have LADA.
- Slower onset than type 1 dm.
- Positive antibodies.
- Low or no c-peptide
- No family history

MODY

- Maturity Onset Diabetes of the Young
- A collection of many (at least 6) inherited diseases affecting insulin secretion.
- Dominant inheritance characteristics
- Normal insulin sensitivity
- Impaired insulin secretion (but still some).
- Diagnosis confirmed by genetic testing.

Pancreatic Diabetes

- Results from a failure of the pancreas as a whole.
  - Loss of both alpha- & beta-cell function
- May be secondary to ETOH abuse, trauma, repeat pancreatitis.
- Exocrine pancreas generally fails before endocrine pancreas.
- Will likely need pancreatic enzyme replacement as well as insulin.

Treatment of Atypical Diabetes

Treatment of Type 1B

- Fluctuating endogenous insulin production will result in wide variations of exogenous insulin demand for first 2-3 years.
- Basal insulin (glargine, detemir, BID NPH) requirements may be lower than in type 1A.
- Due to age & gender of patients, adherence may be low.

Treatment of LADA

- Treat as type 1A
- Basal-bolus insulin regimen
- May require a shift towards pre-prandial and away from basal insulin due to patient's age.
  - Elderly patients may adapt to type 1 diabetes poorly.
  - Older patients may have more sporadic eating habits.

Treatment of MODY

- Treat as type 1A.
- Generally older teens, may not adapt well to the diagnosis.
- Monitor for "insulin bulemia"
  - Especially in teenaged girls
- Genetic counseling should be offered
  - 100% chance of all offspring having MODY

Treatment of Pancreatic Diabetes

- Patients will typically need pancreatic enzyme replacement.
- Loss of glucagon production requires:
  - Glucagon rescue availability
  - Smaller pre-meal bolus doses
  - Smaller bedtime NPH doses
  - NPH may be superior to 24-hour basal regimens
    - Give more in AM, less in PM, to avoid nocturnal hypoglycemia.

Laboratory Tests to Differentiate Types of Diabetes

C-Peptide

- The amino-acid chain cleaved in the conversion of pro-insulin to insulin.
- Indicates endogenous insulin production.
- Should be measured when glucose is elevated (>200 mg/dl).
  - Also known as a "stimulated C-peptide".

Beta-cell antibodies

- "GAD antibodies" are most clinically relevant.
- Positive GAD antibodies are absolute predictor of type 1A diabetes & LADA.
- Will not be present in any other type of diabetes.
- Will return to "undetectable" 8-10 years following onset of disease.

Drug-induced Diabetes

Drug-induced Diabetes (DID)

- Many agents that increase body weight will lead to eventual diabetes (mimicking type 2 diabetes).
- Drug-induced diabetes mimicking type-1 is much less common.
- With only a very few exceptions, drug-induced diabetes will correct when the offending agent is discontinued.

DID mimicking type 2

- Shares same risk factors as for type 2 DM:
  - HTN, hyperlipidemia, family history (ethnic risks), history of GDM, obesity, physical inactivity.
- Treat by changing offending agent if possible.
  - Many times risk of disease being treated is greater than the risk of diabetes (psychosis, AIDS, etc).
- Drug therapy for type-2 DID is typically metformin ± SU or insulin.
- Less likely to kill the patient than type-1 DID.

Medications commonly associated with type 2 DID

- Glucocorticoids:
  - High doses and long term use ↑risk.
  - ↑gluconeogenesis, ↑insulin resistance, ↑weight gain.
  - Much lower incidence for inhaled products (but not zero risk).
  - May account for >50% of all DID.
- Atypical Antipsychotics:
  - ↑insulin resistance, ↑weight gain.
  - Same relative rates as with weight gain.

Medications commonly associated with type 2 DID (2)

- Nucleoside reverse transcriptase inhibitors:
  - AZT, ddC, d4T, 3TC, and abacavir
  - Excluding didanosine
  - ↑insulin resistance, ↑weight gain.
  - Rarely permanent due to concurrent pancreatitis.
- Human growth hormone:
  - ↑insulin resistance, ↑weight gain.

Classes of medications less commonly associated with type 2 DID

- Beta-agonists:
  - ↑gluconeogenesis & glucogenolysis
  - ↓insulin sensitivity
- Beta-blockers:
  - ↓insulin secretion
  - Less likely to happen with B-1 selective agents.
- Diuretics:
  - Low potassium will inhibit insulin release
- Megesterol acetate:
  - ↑insulin resistance, ↑weight gain.
- Niacin:
  - ↑insulin resistance, ↑gluconeogenesis.

Antipsychotics and DID

- Sedentary lifestyle and poor food choices are components of psychosis.
- Hyperglycemia does not appear to be dose related.
- Different agents have different weight profiles:
  - Clozapine > Olanzapine > Quetiapine > Risperidone/Paliperidone > Aripiprazole > Ziprasidone
- Hyperglycemia can occur regardless of weight gain status.

DID mimicking type 1

- Pentamidine
  - Often concurrent with pancreatitis
  - May be irreversible (most likely irreversible of any DID).
  - Directly toxic to pancreatic beta-cells.
- Tacrolimus
  - ↓insulin secretion with or without beta-cell death
  - Difficult to differentiate from steroid-induced diabetes (since most patients on both).

DID mimicking type 1

- Cyclosporine
  - Less common than with tacrolimus
  - Less likely irreversible than with tacrolimus
- Phenytoin
  - Rarely occurs
  - Reversible
- Interferons:
  - Rare, but irreversible beta-cell death due to antibody formation.

DID mimicking type 1 (continued)

- Phenytoin
  - Rarely occurs
  - Reversible
- Interferons:
  - Rare, but irreversible beta-cell death due to antibody formation.
- Gatifloxacin:
  - Unknown mechanism, but mimicks type 1 (fast onset w/ insulinopenia).
  - Reversible.
  - Cipro can inhibit glyburide metabolism and cause hypoglycemia.
  - Gatifloxacin removed from market in 2006.

Strategies to avoid DID

- Obtain baseline FPG before starting agents likely to cause DID.
- Monitor FPG again at 1 month, and q3-6 months thereafter.
- Monitor body weight at each visit. Greater than 5kg weight gain should be evaluated as strong risk regardless of changes in FPG.
- Inquire about symptoms of hyperglycemia at each visit. Symptoms often lag after FPG.

Bibliography

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Question 1

- By what mechanism do corticosteroids induce hyperglycemia?
  - Destruction of pancreatic beta-cells
  - Increased gluconeogenesis
  - Weight gain
  - B & C
  - All of the above

Question 2

- Which of the following nucleoside reverse transcriptase inhibitors (NRTI) is **LEAST LIKELY** to cause hyperglycemia?
  - Didanosine
  - Zidovudine (AZT)
  - Abacavir
  - Lamivudine (3Tc)

Question 3

- The production of what glucose regulatory hormone is <u>unimpaired</u> in autoimmune type 1 diabetes, but is often <u>impaired</u> in pancreatic diabetes.
  - Amylin
  - Insulin
  - Glucagon
  - GLP-1
  - A & D

Question 4

- A Caucasian female patient is diagnosed with diabetes at age 19. Her mother has diabetes and all six of her older siblings were also diagnosed with diabetes between the ages of 17 & 22. She is not pregnant. She has no positive GAD antibodies and a low C-peptide. What type of diabetes is it most likely that she has?

- LADA
- Type 1A diabetes
- Type 1B diabetes
- MODY
- Type 2 diabetes

Question 5

- For the patient in Question 4, which of the following treatment plans is most appropriate?
  a. She should receive counseling regarding the risk of her genetic children having diabetes.
  b. She should be treated with insulin therapy regimen similar to type 1A diabetes.
  c. She should be closely monitored for insulin bulemia.
  d. All of the above are correct