Type 1 Diabetes Mellitus: Clinical Pearls to Accompany Concept Map

What is Type 1 Diabetes? Insulin deficiency following destruction of insulin-producing cells of the pancreas (beta cells)

Epidemiology:

- Age of presentation has bimodal distribution: 4-6 years and then early puberty (10-14 years)
- Genetic susceptibility (risk of developing T1DM is significantly increased in close relatives of patients with T1DM)
    - Increased risk is consequence of polymorphism in multiple genes, including certain HLA types, CTLA-4, etc
    - Risk in general population: 0.5%
        - Risk in identical twin is < 40%
        - Risk in sibling is 4% by age 20
- Second most common chronic illness in pediatrics (1 in 400 kids)
- Patients are at increased risk of other autoimmune diseases

How does the disease present?

- Classic new onset: chronic polydipsia, polyuria, weight loss with hyperglycemia and ketonemia (or ketonuria)
    - Polyuria occurs when glucose level is > 180 mg/dL
        - The proximal tubule can only reabsorb a limited amount of glucose (~375mg/min) which amounts to serum levels of about 160-180 mg/dL and after this level glucose is excreted into urine (glucosuria)
        - Glucosuria causes osmotic diuresis (water follows sugar) which leads to dehydration and hypovolemia
        - Patients have nocturnal enuresis or even daytime incontinence (red flag symptom in children who were previously toilet trained!)
    - Polydipsia occurs because of increased serum osmolality from hyperglycemia and hypovolemia
    - Weight loss results from hypovolemia and increased catabolism
        - Insulin deficiency impairs glucose utilization in skeletal muscle and increases fat and muscle breakdown
- Diabetic ketoacidosis (See below)
- Silent (asymptomatic) incidental discovery

Diagnostic criteria:

1. Glucose >= 200 mg/dL plus symptoms
2. Fasting (8 hour) glucose level >= 126 mg/dL
3. Two hour post-prandial glucose level >= 200 mg/dL
4. Hemoglobin A1C (measure of glucose levels over last 3 months) >= 6.5%
    a. Caveat: cannot use hemoglobin A1C in patients who have abnormal hemoglobin level or rapid destruction of red blood cells; for example, in patients with sickle cell disease.

Supplementary labs during diagnosis:

1. Insulin antibodies: GAD (glutamic acid decarboxylase), IA2 (insulinoma-associated protein 2), insulin Ab, zinc transporter (positive in approximately 90% of patients)
2. Urinalysis (detect glucose and ketones in urine)

3. Beta hydroxybutyrate (type of serum ketone)

What is DKA (diabetic ketoacidosis):

1. Definition: presence of all of following
    a. Hyperglycemia (blood glucose > 200 mg/dL)
    b. Metabolic acidosis: venous pH < 7.3 or serum bicarbonate < 15 mEq/L
    c. Ketosis: presence of ketones in blood (> 3 mmol/L beta-hydroxybutyrate) or urine ketones (moderate or large ketones)
2. Severity is categorized by degree of acidosis
    a. Severe: venous pH < 7.1, bicarbonate < 5
    b. Moderate: venous pH 7.1-- 7.2, bicarbonate 5-9
    c. Mild: venous pH 7.2-- < 7.3, bicarbonate 10-15

Pathogenesis of DKA

1. Absolute insulin deficiency leads to an increase of counterregulatory hormones (glucagon, catecholamines, cortisol, growth hormone)
2. Increase of those hormones leads to:
    a. Lipolysis → breakdown of lipids into fatty acids and glycerol, which are then brought to liver and converted into ketones (acetone and beta-hydroxybutyrate)
        i. Acetone is what is measured in urine; beta-hydroxybutyrate is measured in blood
        ii. Even a small amount of insulin can suppress ketone production (why patients with T2DM rarely present with DKA)
    b. Proteolysis (and decreased protein synthesis) → breakdown of proteins into amino acids and lactate, which are brought to liver and used for gluconeogenesis which leads to even more glucose
    c. Glycogenolysis in liver produces even more glucose
    d. Decreased glucose uptake/utilization (absence of insulin) leads to hyperglycemia
3. Increased glucose leads to osmotic diuresis and loss of water and electrolytes → dehydration and acute kidney injury

Treatment of DKA

1. Fluid resuscitation
    a. Hours 1-2: 10 cc/kg (to 20 cc/kg if severely dehydrated)
    b. Hours 3+: replace at even rate over 26-48 hours
        i. 1.5-- 2x maintenance requirement
    c. If serum [Na+] does not appropriately increase as plasma glucose decreases, do not decrease [Na+] content of fluids
    d. Do NOT replace urine output
2. Electrolyte repletion:
    a. Potassium goal is 3.5 to 4.5 mEq/L
        i. If serum K is < 5 mEq/L → add 40 mEq/L to fluids
        ii. If serum K is >= 5 → do not add K to fluids
    b. Dextrose: avoid hypoglycemia so add 5% dextrose when plasma glucose is 25-300 mg/dL
3. Insulin
    a. Do not give insulin right away! Blood glucose will drop dramatically with fluids alone

b. Standard rate of 0.1 unit/kg/hr (low dose 0.05 unit/kg/hr can be considered if mild DKA or young child, hypokalemia or hyperglycemic hyperosmolar state/HHS)
c. Stop continuous insulin when acidosis has been corrected: pH >=7.3, bicarbonate is >= 15, anion gap is normal (12+/- 2), beta-hydroxybutyrate is 0.5 mmol/L
    i. Patient must be able to eat/drink
    ii. Give rapid acting subcutaneous insulin >= 15 minutes before meal and stop insulin infusion 30 minutes later

Cerebral edema during DKA

- Pathophysiology: mainly due osmotic changes and fluid shifts but also thought to be secondary to fluctuation in cerebral brain flow and inflammatory state
- Risk factors for cerebral injury: severe acidosis at time of presentation, greater degree of hypovolemia
- Symptoms emerge during treatment for DKA (usually between 3 to 12 hours) but can even be present prior to therapy initiation
    - Symptoms: ALTERED MENTAL STATUS
- Treatment: mannitol is first line followed by hypertonic saline (3%) if no improvement

Brief aside on hyperglycemic hyperosmolar state

- Not usually seen in patients with T1 DM
- Distinguished from DKA by absent to mild ketosis
    - Marked hyperglycemia (glucose > 600 mg/dL)
    - Minimal acidosis (venous pH > 7.25 or arterial pH > 7.3 and serum bicarbonate > 15 mmol/L)
    - Marked elevation in serum osmolality
- Altered consciousness
- Severe dehydration and electrolyte losses
- Treatment: more vigorous initial rehydration (versus in DKA) and DO replace urine output, treat with fluid alone until plasma glucose is no longer decreasing then treat with insulin drip at 0.025 to 0.05 unit/kg/hr

Physical exam findings (in DKA)

- Kussmaul respirations: rapid breathing because trying to compensate for metabolic acidosis by breathing off carbon dioxide
- Fruity breath because of ketones
- Thin, dehydrated appearing
- Versus typical physical exam finding in T2DM:
    - Signs of insulin resistance: acanthosis nigricans, hypertension, obese and older patient population

Management? REPLACE INSULIN

- Goal according to the American Diabetes Association is to target glycemic control to prevent vascular complications while avoiding hypoglycemia
- It is a balancing act!
- Patients REQUIRE insulin for survival (versus Type 2 DM)
- 4 different types of insulin

- Rapid acting: Humalog (lispro), Novolog (aspart), Apidra (glulisine)
  - Onset < 15 minutes, peak 60-90 minutes, duration 3-5 hours
- Short acting: Regular insulin
  - Onset 30-60 minutes, peak 2-5 hours, duration 6-8 hours
- Intermediate acting: NPH
  - Onset 1-2 hours, peak 4-12 hours, duration 18-24 hours
- Long acting: Lantus (glargine), Levemir (detemir)
  - Onset 1-2 hours, no peak, duration: 20-24 hours