Type 1 & 2 Diabetes Mellitus

Carisse Orsi, M.D.
Division of Pediatric Endocrinology & Diabetes
UT Health Science Center at San Antonio

Objectives
- Discuss prevalence, basic pathophysiology, comorbidities, and treatment of Type 1 and Type 2 Diabetes in children
- Discuss the medications and modes of treatment for Type 1 and Type 2 Diabetes
- Discuss case scenarios for the Pediatric intern and upper level on the Inpatient service

SEARCH Study - 2009

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Prevalence</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>White</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1DM</td>
<td>2/1000</td>
<td>23/100,000</td>
</tr>
<tr>
<td>T2DM</td>
<td>0.2/1000</td>
<td>4/100,000</td>
</tr>
<tr>
<td>Hispanic</td>
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<tr>
<td>T1DM</td>
<td>0.8/1000</td>
<td>14/100,000</td>
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<tr>
<td>T2DM</td>
<td>0.5/1000</td>
<td>13/100,000</td>
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<tr>
<td>AA</td>
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<tr>
<td>T1DM</td>
<td>0.6/1000</td>
<td>16/100,000</td>
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<tr>
<td>T2DM</td>
<td>1/1000</td>
<td>19/100,000</td>
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<td>Navajo</td>
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<td>T1DM</td>
<td>0.3/1000</td>
<td>3/100,000</td>
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<tr>
<td>T2DM</td>
<td>2.5/1000</td>
<td>35/100,000</td>
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<tr>
<td>Asian</td>
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<tr>
<td>T1DM</td>
<td>0.5/1000</td>
<td>7/100,000</td>
</tr>
<tr>
<td>T2DM</td>
<td>0.5/1000</td>
<td>12/100,000</td>
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</table>

Incidence of DM in San Antonio

Type 1 Diabetes

Juvenile-onset diabetes mellitus
Insulin-dependent diabetes mellitus (IDDM)

Pathophysiology of T1DM
- Develops when environmental triggers stimulate an autoimmune reaction against pancreatic beta cells in a genetically susceptible individual
- Environmental Triggers
  - A number of toxins, dietary components, and viral infections have been proposed
Pathophysiology of T1DM

- Genetic Susceptibility
  - Major histocompatibility complex on chromosome 6
    - DR3-DQ2, DR4-DQ8 alleles increase risk
    - DR2-DQ6 allele is protective
  - Risk for diabetes is increased in relatives
    - 5% in siblings and offspring
    - 25% in identical twins

Pathophysiology of T1DM

- T-cell mediated autoimmune destruction of beta cells
  - Glutamic acid decarboxylase (GAD) Ab
  - Islet cell Ab
  - Detected months to years prior to onset
  - Positive Antibody levels does not infer they will develop diabetes

Pathophysiology of T1DM

- Hit threshold of pancreatic dysfunction over months to years
  - 80% destruction
  - Results in insulin deficient diabetes
  - Honeymoon period
    - Lasts several months to a year or more

Review of Insulin Physiology

- Insulin released by dietary intake
  - Released from the β-cells in a pulsatile fashion
  - These bursts are thought to be the main mechanism for basal insulin

Insulin Physiology

- After a meal, insulin secretion is believed to be increased by both the mass and frequency of the pulses
  - Glucagon-like peptide 1 and its analogs also are released to dietary carbohydrates

Insulin Deficiency

- Results in hyperglycemia
  - Impaired peripheral glucose uptake
  - Increased hepatic glucose production (increased rate of glycogenolysis and rate of gluconeogenesis)
  - Hyperlipidemia results from increase in the mobilization of preformed fat in adipose tissue
Insulin Deficiency
- Counter-regulatory hormones are increased:
  - GH, ACTH, cortisol, glucagon, & catecholamines
  - Worsens hyperglycemia, hyperlipidemia and ketogenesis

Acidosis
- Increased ketone production
- Decreased renal clearance results in a buildup of excretable organic acids
- Accumulation of lactic acid from anaerobic metabolism of peripheral tissues

Acidosis
- Excess ketones (esp. beta hydroxybutyrate) cause nausea and vomiting
- Exacerbates the electrolyte disturbances
- Acetone causes the fruity breath odor
- Kussmaul breathing (rapid shallow breathing) resp. compensation

Diabetic Ketoacidosis
- Hyperglycemia exceeds renal threshold of glucose absorption
- Osmotic diuresis develops due to the glycosuria
- Eventually develop severe dehydration, thirst, tissue hypoperfusion
- On lab analysis will have a low bicarb and pH

Type 2 Diabetes
Body Mass Index (BMI)

- Definition: Weight in kilograms divided by height in meters squared (kg/m²)
- In adults
  - > 25 kg/m² overweight
  - > 30 kg/m² obese
- In children
  - > 85th percentile overweight
  - > 95th percentile obese

5yo boy
3’8” (110 cm) 50% ht
66 lbs (30 kg) 97% wt
BMI 20.0 >95%

Obesity Trends* Among U.S. Adults
(*BMI >30, or about 30 lbs overweight for 5’4” person)

Acanthosis Nigricans
Acanthosis Nigricans
- Indication of DM risk, not DM
- Children should be screened for Diabetes, especially if positive sx
  - ADA recommends fasting glucose
  - Recommend 2 hr OGTT
- Hyperlipidemia (40-50%)
- Hypertension (3-5%)

T2DM Pathophysiology
- β-cell dysfunction
  - Impairment of 1st phase insulin secretion
- β-cell glucotoxicity
  - Paradoxical inhibitory effect of glucose on insulin release
- Hypersecretory insulin release from inherited or acquired β-cell defect or response to peripheral insulin resistance

Pathophysiology of T2DM
- Obesity
- Insulin Resistance
- Impaired Glucose Tolerance
- Dysmetabolic Syndrome
- Diabetes Mellitus

T1DM vs. T2DM
- **T1DM**
  - Thin
  - Pre-pubertal
  - No family hx
  - Positive Ab
  - Caucasian
- **T2DM**
  - Overweight
  - Pubertal or post-pubertal
  - Positive family hx
  - Negative Ab
  - Hispanic, African-American, Native American

Diagnosis of Diabetes
- Symptoms –
  - Polyuria, polydipsia, polyphagia
  - Re-emergence of bedwetting
  - Weight loss
  - Malaise, fatigue
Diagnosis of Diabetes

- ADA criteria
  - With symptoms
    - Random glucose > 200 mg/dL
  - Without symptoms
    - Fasting glucose > 126 mg/dL
    - Blood glucose > 200 mg/dL after 2hr OGTT

Oral Glucose Tolerance Test (OGTT)

<table>
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<tr>
<th>75 g. glucose load</th>
<th>Blood Glucose (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fasting</td>
</tr>
<tr>
<td>Normal</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Impaired fasting glucose</td>
<td>100-125</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>140-200</td>
</tr>
<tr>
<td>Diabetes</td>
<td>&gt; 126</td>
</tr>
</tbody>
</table>

Hemoglobin A1c

- In 1979 methods to measure glycosylation were revolutionized
- “the test that doesn’t lie”...
- Gold standard test uses liquid chromatography for the measurement of glycosylated hemoglobin

Role of A1c in Diagnosis

- Hemoglobin A1c
  - 3 month measure of average blood glucose
  - \([A1c \times 30] – 50 = \text{avg. blood glucose (mg/dL)}\)
  - A1c > 6.5% (145 mg/dL)
  - Confirm with repeat A1c unless symptoms or glucose > 200 mg/dL

New 2010 Guidelines

- “pre-diabetes”- out
- “Categories of increased risk for diabetes”
- A1c range of 5.7-6.4% included as a category for increased risk for future diabetes

Auto-antibodies in Diabetes

- From ongoing national studies 15% of clinically T2DM patients have positive auto-antibodies
- Even if you suspect T2DM, patients with A1c > 8.5-10% need insulin as initial treatment
Type 1 or Type 2

- No exact test can differentiate
- Although T1DM patients have a honeymoon period they cannot survive without insulin
- T2DM patients usually are started on insulin but can eventually be switched to only oral medications

Medications used in Diabetes

- Insulin
- Oral hypoglycemics
- Incretin mimetics

Insulin

- Insulin was discovered in 1921
- Three major groups of insulin preparations
  - Insulin extracted from the pancreases of cows/pigs
  - Human insulin produced from recombinant DNA technology
  - Insulin analogs (molecular modifications that change the pharmacokinetics)
Application of Basal Therapy

- Basal Therapy
  - Glargine, Detemir
  - Dosed based on wt & pubertal staging
  - Normally given in the evening
    - Can be given in the morning or
      anytime of the day as long as given
      consistently at that time

Application of Bolus Therapy

- Bolus Therapy
  - Lispro, Aspart, Glulisine
  - Composed of Carb Ratio and Correction Factor
  - Based on wt and pubertal staging

Bolus Insulin

- Insulin Sliding Scale aka Correction factor aka sensitivity factor
  - 1500/Total daily insulin
  - Eg. TDI=15, 1500/15=100
  - 1 unit for each 100 BG over 200
- Carbohydrate ratio aka carb ratio
  - 500/Total daily insulin
  - 500/15=33
  - 1 unit for each 30 g. of carbs

Application of Bolus Therapy

- Carb Ratio
  - Calculates insulin needed to cover carbohydrates eaten
  - Ex. 1 unit of Aspart for every 15 grams of carbs eaten

Insulin Needs by Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Total Daily Insulin Needs</th>
<th>Basal Insulin</th>
<th>Carb Ratio</th>
<th>Correction Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toddler</td>
<td>0.5 units/ kg</td>
<td>0.25 units/ kg</td>
<td>1 unit for every 30 grams</td>
<td>1 unit for each 100 BG &gt; 200 mg/dL</td>
</tr>
<tr>
<td>Pre-pubertal Child</td>
<td>0.5 units/ kg</td>
<td>0.25 units/ kg</td>
<td>1 unit for every 15 grams</td>
<td>1 unit for each 50 BG &gt; 150 mg/dL</td>
</tr>
<tr>
<td>Pubertal Child/ Teenager</td>
<td>1 unit/ kg</td>
<td>0.5 units/ kg</td>
<td>1 unit for every 7-10 grams</td>
<td>1 unit for each 30 BG &gt; 120 mg/dL</td>
</tr>
</tbody>
</table>
Application of Bolus Therapy

- Sliding Scale
  - Calculates insulin needed to correct an elevated blood sugar back into appropriate range
  - Ex. 1 unit of Lispro for every 50 > 150 mg/dL pre-prandial glucose

  151-200 +1 unit
  201-250 +2 units
  251-300 +3 units...

Example of Basal/Bolus Therapy

- Joe is getting ready to eat lunch
  - Ham sandwich, small apple, 8 oz skim milk = 60 grams of carbs
  - Carb ratio 1 unit:15 grams of carbs
  - Pre-lunch blood glucose is 180 mg/dL
  - Correction is 1 unit: 50 > 150 mg/dL
  - He received a total of 5 units of rapid-acting insulin
    - 4 units for carbs, 1 unit for hyperglycemia

Delivery Methods of Insulin

- Replace insulin via subcutaneous injection/pump
- Other Delivery Methods Investigated
  - Inhaled insulin
  - Oral insulin
  - Transdermal insulin
  - Transplant: Whole/partial pancreas or Islet cell
  - Artificial Pancreas

Delivery of Insulin

- Pens
  - Disposable & reusable
  - Short pen needles
  - 2 unit air shot prior to drawing up dose

Insulin Pumps

- Continuous Subcutaneous Insulin Infusion (CSII)
  - Gives continuous low dose of fast-acting insulin to supply basal insulin needs
  - 80% of typical long-acting insulin dose
Insulin Pumps

- Allows flexibility to set variable basal dosing as well as variable carb ratios and correction factors

Basal:  
- MN 0.8 units/hr  
- 3AM 1.0 units/hr  
- 8AM 0.7 units/hr  
- 8PM 0.8 units/hr

Amylin Replacement

- Hormone co-secreted with insulin from β cell
- Inhibits glucagon secretion
- Slows gastric emptying
- Promotes satiety, decreased caloric intake, and weight loss
- Pramlintide Acetate
  - Subcutaneously injection prior to meals
  - Require reduction of pre-meal insulin
  - Increase risk of hypoglycemia
Primary Treatment: TDM1 vs. TDM2

**TDM1**
- Insulin
- Monitoring
- Intake
- Activity

**TDM2**
- Intake
- Activity
- Monitoring
- Medication

Treatment of T2DM

- Diet and exercise
- Metformin
- Insulin
- Sulfonylureas
- TZDs
- Exenatide

Lifestyle Modifications

- **Decrease Energy In**
  - More water, omit liquid sugar, skim milk
  - More whole fruit and vegetables
  - Portion Sizes
  - Restrict fast food, junk foods

- **Increase Energy Out**
  - Recommend 60 min vigorous physical activity daily
  - Limit TV, computer, video games to 2 hrs daily

Metformin

**MXN of Action:**
- Decreases hepatic glucose output
- Decreases intestinal glucose absorption
- Increases peripheral glucose uptake

**Side-effects:**
- GI side effects
- Risk of lactic acidosis so discontinue when admitted for DKA

Thiazolidinediones (TZDs)

- Pioglitazone, Rosiglitazone

**MXN of Action:**
- Peroxisome proliferator-activated receptor γ modulators directly affect gene expression
- Increase insulin sensitivity of muscle, fat, liver
- Increase in adiposity with reduction in visceral fat
- Improve lipid profiles
- Good evidence of preserving B cells

**Side-effects:**
- Weight gain, fluid retention
Incretin Mimetics
- Exenatide: SQ pre-prandial, B.I.D.
- Liraglutide: SQ Once weekly
  MXN of Action:
  - Enhances glucose-dependent insulin secretion
  - Suppresses glucagon
  - Promotes Satiety/Weight loss
  - Evidence of β cell preservation
  Side-effects: Pancreatitis? Thyroid C-cell tumors in animals?

Sulfonylureas
- Glyburide, Glimepiride, Glipizide
  MXN of Action:
  - Stimulates insulin secretion from beta cells
  Side-effects:
  - Hypoglycemia
  - Weight gain

Treatment Goals
- Preschool-age children 7.5-8.5%
  - Fasting and pre-prandial 100-180 mg/dL
  - Bedtime or overnight 110-200 mg/dL
- School-age children < 8%
  - Fasting and pre-prandial 90-180 mg/dL
  - Bedtime or overnight 100-180 mg/dL
- Teenagers < 7.5%
  - Fasting and pre-prandial 90-130 mg/dL
  - Bedtime or overnight 90-150 mg/dL
- Adult and T2DM < 7%

Diabetic Complications
Outpatient Management

Sick Day Management
- Check urinary ketones when ill or with persistent hyperglycemia (BG > 250 mg/dL)
- Urine ketones signify insulin deficiency
- Replace insulin with q2hr correction until ketones cleared
- Give extra fluids
  - 0.5-1oz/ yr of age/ hr
Hypoglycemia

- Normally treat if <70 mg/dL
- Sx
  - sweating, trembling, hunger
  - palpitations
  - headache, lightheadedness
  - seizures

Hypoglycemia

- Treatment
  - Mild-to-moderate hypoglycemia
    - 15 g. oral glucose
    - (ex. 4 oz of juice or soft drink)
  - Severe hypoglycemia
    - Glucagon: 0.5-1 mg IM or subQ

Diabetic Complications

- Long-term complications include
  - Macro vascular
    - Cardiovascular disease
    - Stroke
  - Micro vascular
    - Renal failure
    - Retinopathy (5-10 yrs)
    - Neuropathy (4-5 yrs)
  - Rarely seen in children and risk can be reduced with proper glycemic control

Diabetic Complications

- Yearly Labs
  - fT4, TSH
  - Urine microalbumin
    - Age 10 yrs or has had DM for 3-5 years for T1DM & at dx for T2DM
  - Fasting lipids
    - Treat children for LDL > 130 mg/dL
    - Goal is to achieve LDL < 100 mg/dL
    - 2008 revision of AAP lipid management guidelines

Monitoring

- Annual Eye Exam
  - At age 10 y.o.
  - DM for 3-5 years
- Labs to consider
  - Celiac screen
  - AM cortisol
  - Gonadal failure screen

Monitoring

Diabetic Complications

Inpatient Management
New Onset

- Consider what type of diabetes from history and physical
- Initial labs would you order?
- Medications should be started?
- Fluid replacement?
- What are you going to tell the family?

Diabetic Ketoacidosis

- Initially, reassess whether they are stable enough to be treated on the floor
- Transfer to ICU if they require an insulin drip
- Can give subQ insulin 0.05-0.1 units/kg/hr with rapid acting insulin following accuchecks
- Goal drop BG ≤100 mg/dL/hr

Electrolyte Disturbances

- K+ may drop after insulin administered due to the extracellular shift
  - Total body insulin is low
  - HypoMg can worsen K+ loss
  - Almost always add K+ to the fluids

Electrolyte Disturbances

- Hyperchloridemia can exacerbate metabolic acidosis
- Pseudohyponatremia
  - Osmotic effect of glucose drawing water into vascular space
  - Na corrected upward 1.6 mEq/L for every 100 mg/dL glucose over 100 mg/dL

Diabetic Admitted to the Inpatient floor

- Hyperglycemia
  - Sliding scale
  - May need to correct every 1-2 hours
- Hypoglycemia
  - Always have an order for the nurses
  - Ex. 15 grams of carbs for blood glucose under 70 mg/dL, then notify the house officer, and recheck blood glucose 30 minutes after administration of carbs

Cerebral Edema

- Pt initially alert but may become drowsy and complain of a headache
- Occurs 1% of DKA, ½ deaths in children with diabetes
- Exact cause not known but believed to be secondary rapid hydration and tx to decrease BG
- Tx with Mannitol, transfer to ICU
Case 1:
- Santa Rosa ED calls you with a new-onset diabetic
- H. P. is a 10 yo male, 30 kg, 1 month history of weight loss, 3 days nausea/vomiting, delusions of being a wizard
- Glucose "High", +urinary ketones, pH: 7.2, sodium 132, bicarb 14, K+ 3.5

Case 2:
- 14 y.o. AA male came to the ED for vomiting
- Glucose 454 mg/dL, pH 7.25, bicarb 17, nl electrolytes
- FHx of type 2 diabetes
- PE: BMI >95% and acanthosis nigricans

Case 3:
- 13 y.o. female with a PMH significant for Cystic Fibrosis, pancreatic exocrine dysfunction and poor weight gain
- A1c is 6%
- Fasting Blood glucose 120 mg/dl
Case 3: CFRD

- Order OGTT as outpatient
- As inpatient obtain 2-hour post-prandial BG
- A1c is only helpful if elevated
  - Can be falsely low with CF due to chronic hypoxia

1st line usually long-acting insulin or NPH for patients on G-tube feeds

2nd line is a rapid-acting insulin usually with a sliding scale

Patients are more sensitive to insulin therapy so we dose less aggressively

Avoid oral hypoglycemic medications

Rarely develop DKA

Main treatment goal is to maximize calories

Questions?

References