Management of Type 1 Diabetes
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Dr. Carisse Orsi has no relevant financial relationships with commercial interests to disclose.

Objectives
• Discuss basic pathophysiology of the development of Type 1 diabetes
• Discuss the medications and modes of treatment for Type 1
• Discuss case scenarios for the Pediatric intern and upper level on the Inpatient service

Incidence of DM in San Antonio

SEARCH Study - 2009

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Type 1 (per 1000)</th>
<th>Type 2 (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence</td>
<td>Incidence</td>
</tr>
<tr>
<td>White</td>
<td>T1DM 0.2/1000</td>
<td>T2DM 0.5/1000</td>
</tr>
<tr>
<td>Hispanic</td>
<td>T1DM 0.8/1000</td>
<td>T2DM 0.5/1000</td>
</tr>
<tr>
<td>AA</td>
<td>T1DM 1/1000</td>
<td>T2DM 1/1000</td>
</tr>
<tr>
<td>Navajo</td>
<td>T1DM 0.3/1000</td>
<td>T2DM 2.5/1000</td>
</tr>
<tr>
<td>Asian</td>
<td>T1DM 0.5/1000</td>
<td>T2DM 0.5/1000</td>
</tr>
</tbody>
</table>

Source: SEARCH for Diabetes in Youth Study
NHW=non-Hispanic whites; NHB=non-Hispanic blacks; H=Hispanics; API=Asians/Pacific Islanders; AI=American Indians
Epidemiology
- Most cases diagnosed before the age of 18
  - Peaks ages 3-6 years and mid-teens
  - Can present as late as the fourth decade
- Seasonal variation more related to geographic distribution

Back to the Basics
- Energy regulated by the balance between insulin and counterregulatory hormones
  - Glucagon
  - Cortisol
  - Catecholamines
  - Growth Hormone

Insulin Function for Energy Homeostasis
- Promotes uptake of glucose by muscle and adipose tissue
- Inhibits glucose production by the liver
- Inhibits triglyceride release from adipose tissue

Key points
- Brain takes up glucose independently of insulin and other hormones
- Ketones generated from fat breakdown provide an alternative energy source when intracellular energy is low

Autoimmune Destruction
- T-cell mediated autoimmune destruction of the pancreatic β-cells
- Autoantibodies to islet cell antigens develop as a result of the β-cell damage
  - Some antibody-positive people never develop diabetes
- Risk of progression does increase with each positive antibody
**Autoantibodies**

- T-cell mediated autoimmune destruction of beta cells
  - Glutamic acid decarboxylase (GAD) Antibodies
  - Islet cell Antibodies
  - Insulin Antibodies
- Can be detected months to years prior to onset

**Genetics of T1DM**

- Genetic Susceptibility
  - Major histocompatibility complex on chromosome 6p21
    - DR3-DQ2, DR4-DQ8 alleles increase risk
    - DR2-DQ6 allele is protective
- Risk for diabetes is increased in relatives
  - 5% in siblings and offspring
  - 40% in monozygotic and 5% in dizygotic twins

**Multifactorial Genetic disease**

- 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
  - Only significant results found for congenital rubella infection after which up to 20% develop T1DM

**Development of Diabetes: Clinical Presentation**

- Hit threshold of pancreatic dysfunction over months to years
  - 80% destruction
- Eventually develop persistent hyperglycemia
  - Excessive hepatic glucose release
  - Unregulated gluconeogenesis
  - Breakdown of adipose tissue and muscle

**Diagnosis of Diabetes**

- ADA criteria
  - With symptoms
    - Random glucose >200 mg/dL
  - Without symptoms
    - Fasting glucose >125 mg/dL
    - Blood glucose > 200 mg/dL after 2hr OGTT (Requires a

**Oral Glucose Tolerance Test (OGTT)**

<table>
<thead>
<tr>
<th>Blood Glucose (mg/dL)</th>
<th>Fasting</th>
<th>2 hour post-prandial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;100</td>
<td>&lt;200</td>
</tr>
<tr>
<td>Impaired fasting glucose</td>
<td>100-125</td>
<td></td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>140-200</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>&gt; 125</td>
<td>&gt;200</td>
</tr>
</tbody>
</table>
Differential Diagnosis of Hyperglycemia

- Hyperglycemia due to stress
  - No history of polyuria, polydipsia or nocturia
  - A1C should be normal
  - Insulin and C-peptide levels should be elevated
- T2DM or MODY
  - Measure autoantibodies but regardless of results likely need insulin gtt or SQ

HbA1c

- 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
  - \([A1C \times 30] \div 50 = \text{avg blood glucose (mg/dL)}\)
- \(A1C > 6.5\% (145 \text{ mg/dL})\)
  - Confirm with repeat A1C unless symptoms or glucose > 200 mg/dL

Treatment: 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/Bolus Therapy

- Basal Therapy
  - Glargine, Detemir
  - Dosed based on wt & pubertal staging
  - Typically 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 Basal/ Bolus Therapy

• Bolus Therapy
  – Lispro, Aspart, Glulisine
  – Combination of Carb Ratio and Correction Factor
  – Based on wt and pubertal staging

Total Daily Insulin

<table>
<thead>
<tr>
<th>Age Range</th>
<th>kg x Sensitivity Factor</th>
<th>Insulin Needed/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-7 yrs</td>
<td>kg x 0.5</td>
<td>= units/day</td>
</tr>
<tr>
<td>8-11 yrs</td>
<td>kg x 0.6</td>
<td>= units/day</td>
</tr>
<tr>
<td>12-18 yrs</td>
<td>kg x 0.7</td>
<td>= units/day</td>
</tr>
</tbody>
</table>

Bolus insulin

• Insulin Sliding Scale aka Correction factor aka sensitivity factor
  – 1800 /Total daily insulin

• Carbohydrate ratio aka carb ratio
  – 500/Total daily insulin

Application of Basal/Bolus Therapy

• Bolus Therapy/Correction Factor
  • 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, and so on
Application of Basal/ Bolus Therapy

• Carb Ratio
  — Calculates insulin need to cover carbohydrates eaten
  — Ex. 1 unit of Aspart for every 15 grams of carbs eaten

Example:
• 7 yo female with new-onset T1DM
• Wt: 20kg
• TDI (wt x 0.5): 20 x 0.5 = 10
• Sliding scale (1800/TDI) = 180
  — 1 unit for every 180
• Carb ratio (500/TDI) = 50
  — 1 unit for every 50 grams of CHO

Estimate of 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 30-50 grams</td>
<td>1:100 &gt; 200 mg/dL</td>
</tr>
<tr>
<td>Pre-pubertal Child</td>
<td>0.5-0.6 units/ kg</td>
<td>0.25 units/ kg</td>
<td>1 unit for every 15 grams</td>
<td>1:50 &gt; 150 mg/dL</td>
</tr>
<tr>
<td>Pubertal Child/ Teenager</td>
<td>0.7-1 unit/ kg</td>
<td>0.5 units/ kg</td>
<td>1 unit for every 7-10 grams</td>
<td>1:30 &gt; 120 mg/dL</td>
</tr>
</tbody>
</table>

Application of Basal/Bolus Therapy

• Normally given prior to meals
  — Can be given within 20 minutes of starting the meal if amount of food to be consumed questionable

  *some special cases for younger children when we give the shot after the meal

Example of Basal/ Bolus Therapy

• Joe has T1DM with Carb ratio 1:15, Sliding scale 1:50>150mg/dL
  — Ham sandwich, small apple, 8 oz skim milk = 60 grams of carbs
  — Pre-lunch blood glucose is 180 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
  - *there is no basal insulin*

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

Sensor Read Out
Treatment Goals

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

Diabetic Complications
Outpatient Management

Development of Ketoacidosis

• Net loss of total body water with chronic dehydration (polyuria/polydipsia)
• Weight loss from tissue wasting
• Lactic acidosis
• Late stage is rise in counterregulatory hormones

Development of Ketoacidosis

• Rise in glucagon with insulin deficiency that eventually leads to DKA
• Accumulate ketoacids and lactic acid causing metabolic acidosis
• Stimulates respiratory drive (Kussmaul respiration)

Diabetic Ketoacidosis

• Nausea, vomiting and abdominal cramps are a sign of moderate to severe DKA
• Fatigue, lethargy and irritability but oriented and to be able to be aroused
• Coma and disorientation are late signs

Risk factors for DKA

• <2 years of age
• Ethnic minority
• Lack of insurance
• Lower BMI
• Preceding infection

*SEARCH trial reported 29% of pts with T1DM <20 yrs presented with DKA
Mortality and Morbidity

- Cerebral edema accounts for about 50-85% of all DKA deaths
- Other causes include hypoK, hyperK, acute renal failure, hypoglycemia, aspiration, pulmonary edema, infection, neurological complications (thrombosis) and rhabdomyolysis

Defining DKA

- Hyperglycemia (>250mg/dL), pH <7.3 &/or bicarb <15 mmol/L and moderate to large ketones
- Mild Bicarb >15, moderate Bicarb 10-15 and severe <10
- Severe DKA when the Bicarb <10 or the pH is <7.2

Acute Management of Hyperglycemia

- Blood Glucose: >125 fasting with S/S Random >200 A1c >6.4%
- Bicarb<10, pH<7.2
- Bicarb>10-20
- Mild to no s/s, Bicarb>20
- ICU: Insulin Gtt IVFs
- IMC/Floor: IVFs SQ insulin
- Outpatient: SQ insulin

DKA Management Keypoints

- Protocols usually involve rehydration, insulin therapy and glucose delivery
- Saline bolus, repeat if necessary
  - Never exceed 40mL/kg IVFs 1st 4 hrs
- Add K+ to fluids once urine output is established
- Goal to keep Na in upper normal range in 1st 24hrs to avoid rapid osmotic shifts

DKA Management

- Usually start with Regular Insulin 0.05-0.1units/kg/hr
  - Avoid IM/IV rapid insulin
  - Don’t start insulin gtt till about 1 hour of hydration
- Goal to decrease glucose by 50-100 per hour
  - Keep glucose in 200s till the bicarb and GAP correct

DKA Management

- If acidosis persists, consider an underlying illness:
  - Infection
  - Cholelithiasis
  - Hyperchloremic acidosis
Transition from Insulin drip to Injections

- Timing is everything
  - If gtt is stopped at night, give the full dose one hour before stopping the gtt
  - If gtt is stopped in the morning, give ½ the dose in the morning followed by the full dose that night

Pumps in the Hospital Setting

- Pts are usually more compliant
- Risk for DKA if they have pump malfunction in 4-6 hours
- Start same DKA protocol in ICU and transition back to pump if working
- If need to change to SQ, use same Carb and ISS settings on pump
- If admitted to floor for non-DKA issues, continue using the pump

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

Monitoring

- Annual Optho Exam for retinopahty
  - Age 10 yo
  - DM for 3-5 years

- Annual 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

- Labs to Consider:
  - Celiac screen
  - AM Cortisol
  - Gonadal failure screen

Monitoring
Thyroid Abnormalities

- Recommend assessing thyroid function at diagnosis of T1DM and annually thereafter.
- 110 patients (66 males), median age 11.3 yrs at diagnosis of T1DM, were monitored for 2.3 (0.7-4.2) years
- 21/110 (19.0%) pts had abnl thyroid function at dx of T1DM.
  - Of these, 16 had normal thyroid function on reassessment after 45 (3-540) days.
  - Abnormalities of thyroid function occurred more commonly in children with DKA than those who did not have DKA (9/29, 31.0% vs 12/81, 14.8%, p<0.025).
- At the end of the observation period, five (4.5%) patients had minor abnormalities of thyroid function not requiring treatment and three (2.7%) were treated

Clinical Cases

Page from ICU nurse 6am

- DKA admission from 1 am is disoriented and confused

- What do you want do?
  - A. Call the PICU fellow
  - B. Disregard since all DKA pts are confused
  - C. STAT head CT
  - D. Evaluate the pt

Cerebral Edema

- New-onset diabetic pts are at high risk for cerebral edema especially children younger than 5
- Unsere of etiology
  - Possibly rapid changes in hydration or osmolality
  - Bicarbonate treatment
  - Greater BUN at presentation

Cerebral Edema

- Watch for development of headache and mental status changes
- Not necessary to send them to CT
  - Results will not change your management
- Treatment with mannitol at dose up to 1g/kg
- Pts prone to thrombosis so you may consider a stroke with a CNS event

Page from 9th floor

- “Doctor, the patient’s blood sugar is 50 mg/dl. What do you want to do?”
  - A. Call endo pager
  - B. Call upper level
  - C. Repeat with venous blood sugar
  - D. Give 30g juice/soda
Hypoglycemia

- Glucose < 60 mg/dL
  - Normally treat if <70-80 mg/dL
- Sx
  - sweating, trembling, hunger
  - palpitations
  - headache, lightheadedness
  - seizures

Hypoglycemia

- Treatment
  - Mild-to-moderate hypoglycemia
    - 15-30g oral glucose
      - (ex, 4 oz of juice or soft drink)
    - Severe hypoglycemia
      - Glucagon: 0.5-1 mg IM or subQ

Lab calls with critical value: K⁺ 1.9

- Initially, K⁺ was elevated on presentation
- No K⁺ was added to IVFs for DKA pt
- Pt also had hypoMag at presentation

Hyper- & Hypokalemia

- Initially, K⁺ levels may be high
  - May lead to cardiac arrest
- After treatment, K⁺ levels drop from extracellular to intracellular shift
  - May lead to cardiac arrhythmias, ileus and muscular weakness
- HypoMag can exacerbate hypokalemia

Sodium 130 on admission of new-onset DKA

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

Page from ICU nurse that Bicarb is 10

- Pt on DKA protocol for 10 hours with persistent metabolic acidosis
- What are your treatment options?
  - A. Call the PICU fellow
  - B. Look for signs of infection
  - C. Increase insulin gtt and dextrose
  - D. Change IVFs from KCl to Kphos
Page from 9th flood for critical high blood sugar

- 13 yr old female admitted for Cystic Fibrosis exacerbation has a blood sugar of 455mg/dL
  - A1c is 6%; Fasting Blood glucose 120 mg/dl
  - A. Repeat with venous blood sugar
  - B. Transfer to PICU for DKA
  - C. Change to ADA diet
  - D. Start SQ insulin and call Endo pager

CFRD

- Secondary diabetes
- Best treated with insulin vs. oral hypoglycemic medications
- Rarely develop DKA
- Concern for maximizing calories

Summary

- T1DM is a common chronic disease in children with multiple treatment options with insulin therapy
- Follow the guidelines for initiating therapy
- Always feel comfortable call the endocrine pager for any questions
- Dr. Hamaker cell (210)889-210

Questions?

References