Diabetes: We’ve Come A Long Way

Anita Swamy, M.D.
Pediatric Endocrinologist, Children's Memorial Hospital
Medical Director, Chicago Children's Diabetes Center
La Rabida Children's Hospital

Quiz

True or False?
1. Today, diabetes diagnosed in the pediatric population is primarily type 1
2. Type 2 diabetics do not have positive insulin, GAD and islet cell antibodies

Lecture Overview
- History of diabetes and insulin therapy
- Diagnosis
- Pathophysiology and Epidemiology of childhood DM
- Insulin types and action profiles
- Basal-bolus management regimen
- Nutrition and DM
- Pumps and continuous glucose monitoring systems
- Research updates

History of Diabetes
- Origin of the word diabetes mellitus
  - Diabetes = Greek (siphon)
  - Mellitus = Latin/Spanish (sweet)
- 1500 BC:
  - Egyptian and Hindu writings: “a mysterious disease…with flies and ants attracted to the urine of people (affected)”

History of Diabetes
- 1776
  - Dr. Dobson evaporated urine from a patient with diabetes → ‘saccharine materials’ = diagnosis of diabetes.
- Late 1800s
  - While investigating fat digestion, MDs performed pancreatectomies in dogs → animals became diabetic → pancreas was the culprit!
History of Diabetes

Who are these guys? (true rock stars®)

Timeline: Diabetes Discoveries

Diagnosis of Diabetes

Blood Glucose (mg/dL)

- Impaired Fasting Glucose (IFG): 100-125
- Impaired Glucose Tolerance (IGT): 140-199
- Diabetes (Types 1 and 2): Fasting: >/= 126
  OGTT: >/= 200
  Random: 200 + symptoms

Note: HbA1C is now approved as diagnostic tool for type 2 diabetes (Dx = A1C of 6.5)
Fasting blood glucose is another recommended screening tool; OGTT is gold standard

Pathophysiology of T1DM

- Autoimmune destruction of pancreatic beta cells
  - Involves mainly T-cell destruction although we measure auto-antibodies (ICA, IAA, GAD, IA2). These are likely not causative
  - Having more than 1 of above auto-Ab increases risk of T1DM, but only done in clinical trials
  - not recommended as screening tests

Pathophysiology of Type 1 DM

- Environmental factors:
  - Foods and toxins
    - Cow’s milk and beta-casein, vitamin D
  - Viruses
    - Congenital rubella, coxsackie, enterovirus
- Genetics: over 20 known genes
  - Majority related to MHC, chromosome 6
  - DR3-DQ2 and DR4-DQ8 and DR3/DR4 → increased risk for type 1 DM (and other autoimmune dz)
  - DR2-DQ6 allele is protective
Genetics of T1DM

<table>
<thead>
<tr>
<th>Sibling</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>5%</td>
</tr>
<tr>
<td>Identical twin</td>
<td>&lt;0.5%</td>
</tr>
<tr>
<td>HLA identical</td>
<td>19%</td>
</tr>
<tr>
<td>HLA haplotype</td>
<td>6%</td>
</tr>
<tr>
<td>HLA nonidentical</td>
<td>1%</td>
</tr>
<tr>
<td>Offspring</td>
<td>Risks</td>
</tr>
<tr>
<td>Overall</td>
<td>5%</td>
</tr>
<tr>
<td>Father who has IDDM</td>
<td>6%</td>
</tr>
<tr>
<td>Mother who has IDDM</td>
<td>2%</td>
</tr>
</tbody>
</table>

Epidemiology

- Type 1 DM:
  - Affects 1.7 million Americans
  - 30,000 new cases per year; over 13,000 in children
  - Incidence of not only type 2, but also type 1, is increasing across the world
    - Especially in kids under age 5
    - Increase of 3-5% annually = estimated increased incidence of 40% in 2010 vs 1998

Worldwide Incidence Increasing

Age Distribution

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>1.00</td>
</tr>
<tr>
<td>5-9</td>
<td>1.52</td>
</tr>
<tr>
<td>10-14</td>
<td>1.94</td>
</tr>
<tr>
<td></td>
<td>(1.47-1.59)</td>
</tr>
<tr>
<td>5-9</td>
<td>1.00</td>
</tr>
<tr>
<td>10-14</td>
<td>1.72</td>
</tr>
<tr>
<td></td>
<td>(1.64-1.79)</td>
</tr>
<tr>
<td>10-14</td>
<td>1.93</td>
</tr>
<tr>
<td></td>
<td>(1.86-2.01)</td>
</tr>
<tr>
<td>Total</td>
<td>1.00</td>
</tr>
<tr>
<td>5-9</td>
<td>1.62</td>
</tr>
<tr>
<td>10-14</td>
<td>1.94</td>
</tr>
<tr>
<td></td>
<td>(1.85-1.98)</td>
</tr>
</tbody>
</table>

*Adjusted for center
**Adjusted for center and sex.

Pediatric Epidemiological Study

- SEARCH: multicenter study
  - Clinical features, complications, quality of life, epidemiology in children w/DM
  - Six centers in US, 3.5 million children under age 20
    - 6379 with diabetes

Libman I, Songer T, LaPorte R: How many people in the U.S. have IDDM. Diabetes Care 16:841, 1993

The Diamond Project Diabetes Care October 2000 vol. 23 no. 10 1516-1526
Incidence of DM by Age and Race

<table>
<thead>
<tr>
<th>Population</th>
<th>Prevalence (per 1000)</th>
<th>Incidence (per 100k/yr)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic White</td>
<td>T1: 2</td>
<td>T1: 23.6</td>
<td>few T2 &lt;10y</td>
</tr>
<tr>
<td></td>
<td>T2: 8.16</td>
<td>T2: 3.7</td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>T1: 0.27 - 2.04</td>
<td>T1: 10 - 14: 35.8, 15+:19</td>
<td>44% T1 obese</td>
</tr>
<tr>
<td></td>
<td>T2: 15+:2.9</td>
<td>T2: 8-15</td>
<td>T2 low income</td>
</tr>
<tr>
<td>Hispanic</td>
<td>T1: 0.2 - 2.04</td>
<td>T1: 8-15</td>
<td>high A1c &amp; LDL</td>
</tr>
<tr>
<td></td>
<td>T2: 0.1 - 1</td>
<td>T2: 8-15</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>T1: 0.26 - 0.77</td>
<td>T1: 8-15</td>
<td>all T2 &gt; 10y</td>
</tr>
<tr>
<td></td>
<td>T2: 0.52</td>
<td>T2: 12.1</td>
<td></td>
</tr>
<tr>
<td>Navajo</td>
<td>T1: &lt;0.5 all ages</td>
<td>T1: &lt;1 all</td>
<td>poor control depression</td>
</tr>
<tr>
<td></td>
<td>T2: 3.08-3.73</td>
<td>T2: 52-59</td>
<td></td>
</tr>
</tbody>
</table>

SEARCH Data

SEARCH Findings

- Pathophysiology
  - 30% of T2DM with positive antibodies

- Weight
  - Type 1: 30% were obese, and 44% overweight
  - This is significantly higher than in non-diabetics
  - Higher BMI = greater incidence of Type 1!

- Mental health
  - About 10% with depression, same as non-diabetic kids
  - Issues seen in type 2 > type 1

SEARCH Findings

- Cardiovascular Risk
  - About half of participants with LDL > 100 mg/dL, and 20%-40% with LDL > 130 mg/dL
  - Type 2 >> type 1
  - Only 10% met dietary fat intake and fruits/veg intake goals

Insulins and Action Profiles

<table>
<thead>
<tr>
<th>Name</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-Acting</td>
<td>10 min</td>
<td>60 min</td>
<td>3 hrs</td>
<td>Glulisine, Lispro, Aspart</td>
</tr>
<tr>
<td>Short-Acting</td>
<td>30 min</td>
<td>2-3 hrs</td>
<td>6 hrs</td>
<td>“Regular” insulin</td>
</tr>
<tr>
<td>Intermediate-Acting</td>
<td>2-4 hrs</td>
<td>6 hrs</td>
<td>10-12 hrs</td>
<td>NPH (&quot;cloudy&quot;)</td>
</tr>
<tr>
<td>Long-Acting</td>
<td>1 hr</td>
<td>None</td>
<td>24 hrs</td>
<td>Glargine, Detemir</td>
</tr>
<tr>
<td>Pre-Mixed</td>
<td>Minutes and then 2 hrs</td>
<td>Intermediate btw long and short acting</td>
<td>Mixed</td>
<td>Includes 70/30, 50/50, 75/25</td>
</tr>
</tbody>
</table>
**Insulin Action Profiles**

- Aspart, Inspro (4-6 hr)
- Regular (8-20 hr)
- NPH (12-20 hr)
- Glargine (20-24 hr)

**Insulin by Injection: NPH**

- 2 (or 3) daily injections
- Can mix 2 insulins (rapid and NPH)
- Problem is peak of NPH insulin - during the day and overnight

**Insulin by Injection: Basal-Bolus**

- A.K.A. Multiple Daily Injections therapy (MDI)
- 3 injections of rapid acting at mealtime
- 1 injection of long acting

**Basal-Bolus Regimen**

- Basal insulin: (Glargine, Detemir)
  - To calculate dose, start at about 1 unit per kg/day as need, more for pubertal pt and less for under age 10
  - Approximately 50% will be basal requirement at start
  - Given at the same time everyday
  - May be given at school in non-compliant pts

- Bolus: (rapid-acting analog)
  - Given prior to meals containing carbohydrates, usually 3-5 times per day depending upon child’s eating schedule
  - Exception: young children with unpredictable intake may receive injection after meal
  - School-based care and nutrition education are KEY

**Basal-Bolus Regimen**

- TDD = total daily dose

- Bolus:
  - Rapid acting insulin
  - Dose is Based upon two factors

- Pre/End meal glucose: 6-8 mmol/L, given as correction

- This is calculated by adding 1 unit of insulin over per g of carbohydrates

- Insulin needed for correction: (Out BG – In Target BG)/CF

- The amount we expect BG to rise based on carbohydrates eaten

- This is calculated by taking 500 and divide by TDD = insulin to carb ratio

- Insulin needed for Carbohydrates: Total grams of carbs x (Insulin to carb ratio)
Basal-Bolus Regimen

- **Bolus:**
  - Rapid acting insulin: Lispro, Aspart, Glulisine
  - **Dose is Based upon 2 factors:**
    - Pre-meal Blood glucose
    - Carbohydrate content of meal

  - YES, diabetics CAN eat carbohydrates (CHO), and they should, but in moderation and in a consistent manner, by “counting” the CHO content of meals
  - E.g. set as “take 1 unit for every (10, 15, 20, etc.) grams of CHO”
  - Examples of foods and CHO content
  - Approximate number of CHO grams per day that we require

CHO Counting 101

<table>
<thead>
<tr>
<th>Carbohydrates</th>
<th>Serving Size</th>
<th>Grams per Serving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bread, standard slice</td>
<td>1 slice</td>
<td>15 grams</td>
</tr>
<tr>
<td>Rice or Pasta</td>
<td>1/3 cup</td>
<td>15 grams</td>
</tr>
<tr>
<td>Pinto Beans</td>
<td>1/2 cup</td>
<td>15 grams</td>
</tr>
<tr>
<td>Corn or Peas</td>
<td>1/2 cup</td>
<td>15 grams</td>
</tr>
<tr>
<td>Potato</td>
<td>1/2 cup</td>
<td>15 grams</td>
</tr>
<tr>
<td>Peaches</td>
<td>1/2 cup</td>
<td>15 grams</td>
</tr>
<tr>
<td>Cantalope, cubed</td>
<td>1 cup</td>
<td>15 grams</td>
</tr>
<tr>
<td>Milk, lowfat</td>
<td>1 tsp</td>
<td>12 grams</td>
</tr>
<tr>
<td>Jelly</td>
<td>1 tbsp</td>
<td>15 grams</td>
</tr>
</tbody>
</table>

Example Meal

- 1 grilled chicken sandwich (30g)
- 1 ounce pretzels (15g)
- 1 apple (20g)
- 8 oz carton of milk (12g)

Total Carbohydrates = 77 grams

Example

- 12 year old pre-pubertal girl, weighing 40 kg, has resolution of DKA. How do you initiate a basal-bolus regimen
- **Basal:** Assume 1 unit/kg total insulin, 50% as basal. Total is 40 units, and 20 units given as basal once she gets off drip
- The time basal is given can be adjusted later to suit family’s schedule.

Example

- **Bolus insulin: calculating correction factor**
  - First figure out her target: about 80-140
  - Varies by age, clinician but ADA provides goals
  - Then for the correction, divide 1800 by TDD (40) → gives you 45
  - So her correction formula is
    - (Her measured BG – Target of 140) divided by correction of 45
  - If her BG is 185
    - \( \frac{185 - 140}{45} \) = 1 unit for correction
Example
- Bolus insulin: calculating insulin to carb ratio
  - Divide 500 by total daily dose of 50 = 10
  - Her insulin to carb ratio is 1 unit for every 10 grams of carbs eaten
  - If she eats 60 grams: 60 + 10 = 6 units for carbs
- If this child has a premeal BG of 185, and eats a 60 gram carb meal → she needs 1 + 6 = 7 units of rapid-acting insulin for that meal.
- Why go through all this trouble???

Benefits of Intensive Therapy
- Intensive = multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSI or insulin pump)
- Reduced complications
  - DCCT (Diabetes Control and Complications Trial) 1983-1993, and EDIC (Epidemiology of Diabetes Interventions and Complications): follow-up to DCCT
  - Reduced hypoglycemia
    - Diabetes Care 28:950-955, 2005
  - Decreased FBG
    - Diabetes Care 2000 Aug 23(8):1137-42

DCCT: treatment conditions
Conventional group (n = 730):
- Aim: to avoid symptoms of hyper / hypoglycemia
- 1 or 2 insulin injections per day
- Daily self-monitoring
- Initial diet and exercise education
- Quarterly visits

Intensive group (n = 711):
- Aim: symptom-free + HbA1c < 6.5%
- ≥ 3 insulin injections / day or insulin pump
- ≥ 4 daily blood glucose tests
- Hospitalization for initiation
- Comprehensive education program
- Frequent dietary instructions
- Monthly clinic visits

Results of DCCT, EDIC

DCCT Study Findings
- Intensive blood glucose control results in:
  - Retinopathy 76% reduced risk
  - In 13-17 yr olds, 53% reduced risk and 70% reduced progression in those with existing retinopathy *
  - Nephropathy 50% reduced risk
  - Neuropathy 60% reduced risk


Results of DCCT, EDIC

EDIC Study Findings
- Intensive blood glucose control reduces risk of
  - Any cardiovascular disease event by 42%
  - Nonfatal heart attack, stroke, or death from cardiovascular causes by 57%
**Modes of Insulin Delivery**

**Injections**
- Vials and syringes
- Pens

**Insulin Pumps**
- Most physiologic: continuous subcutaneous insulin infusion (CSII)
- ANY patient can go on a pump, if there is sufficient family support, education, and drive
- There is only ONE type of insulin (rapid-acting) but it is programmed to act as a basal insulin as well.
- Same insulin to carbohydrate ratio and correction factor methodology as with the injections

---

**Multiple Injections vs. Pump**

**MDI**
- flexible lifestyle
- long acting insulin on board
- inability to adjust basal insulin within the day
- nothing attached to skin
- no technology failures
- possible calculation errors
- concern for “stacking” insulin
- roughly imitates physiology

**Pump (CSII)**
- flexible lifestyle
- NO long acting insulin on board = more DKA potential!!
- ability to adjust basal insulin within the day
- site/pump on skin & carried near patient
- possible technology failures
- no calculation errors
- “insulin on board” avoids “stacking” insulin
- more precisely imitates physiology

---

**Blood Glucose Monitoring**

**Capillary**
- Self-monitoring of blood glucose (SMBG)
- Fingersticks and alternative sites
- 4+ times per day: before meals, before bedtime, then if feel hyper- or hypoglycemic, 2h postprandial and overnight if concerned or need dose changed

---

**Continuous Glucose Monitoring**

**Interstitial fluid**
- Wear sensor 72-120 hrs
- Glucose measured every 10s, gives average over 5 min
- Gives trends
- Lags behind blood glucose ~ 10-15 min
- Takes 3-12 hrs to calibrate
- Needs fingerstick glucose 2-3 times per day for calibration, + to confirm hyper- or hypoglycemia
- Still new - currently adjunct to SMBG

---

**MDI vs CSII: How to Decide?**

- Checking BG 4+ times per day
  - What is the pattern of BGs: variable, lots of hypoglycemia?
  - Patient preference and education!
  - Age?
  - Schedule and school-based care, exercise?
  - Compliant with appointments
  - Close follow-up
Continuous Glucose Monitors

- Candidates
  - Anyone!
  - Ideal for children with
    - Hypoglycemia (potentially for even those without DM)
    - Erratic BGs
    - Pump tx
    - Noncompliance

Insulin Dose Adjustments

- Emphasis on education and self management, with medical guidance
- Best for families to be able to download, interpret and make changes at home
- Families may download BG meter and/or pump data, as well as sensor

Sample Pump Download

Sample Download

CGMS Sensor Data

Outcomes

- Glycemic control in SEARCH
  - A1c > 7.5% in over 70% of children, regardless of insulin regimen
  - Best outcomes → insulin pump
  - 17% of type 1 and 27% of type 2 diabetics have an A1c of ≥ 9.5%
  - Higher in minority populations
  - Longer duration → higher A1c

The Role of the Pediatrician in Diabetes Management

- We value your input!
- Frequent +/or persistent infections → likely due to poor control
- Inform us if other conditions require treatment which may affect DM (e.g. asthma and steroids)
- Monitor growth and weight parameters
  - Celiac and thyroid disease, Mauriac syndrome

The Future

- Immune modulation
  - AbATE: anti CD3
    - New T1DM pts, one dose at start of trial + 12 mos
      - Decreased insulin requirement at 18 mos vs controls
    - Protégé Trial
      - Mixed results overall but anti CD3 drug effective in preserving b-cell function in kids 8-11, among other grps
    - CTLA4-Ig (cytotoxic T-lymphocyte 4)
      - Treatment grp had increased c-peptide and decreased HbA1c after 2 yrs

The Future: Technology

- Low-glucose suspend systems
  - Approved in 40 other countries
  - FDA on June 20th clarified requirements for approval in US
- Artificial pancreas/closed-loop systems

The Team

Team care from board-certified pediatric endocrinologists, nurse practitioners, CDEs, RNs, dieticians, psychologists and social workers