Update on Childhood Diabetes

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DISCLOSURE

I have no relevant financial relationships with the manufacturers(s) of any commercial products(s) and/or provider of commercial services discussed in this CME activity.

Objectives

- Diagnosis and treatment of T1 DM
- SEARCH Study on Diabetes: epidemiology and diabetes control
- TODAY study on Type 2 Diabetes
Diabetes 101

Case history
- 15 mo old boy born to a 15 y.o. mother
- Polyuria, polydipsia x 2 weeks
- Weight loss of 6 lbs
- Glucose: 789 mg/dl, HCO3 13 mmol/L, venous pH 7.3
Does he have diabetes?

Criteria for diagnosis of Diabetes

1) plasma glucose $\geq 200$ mg/dl
2) Fasting plasma glucose $\geq 126$ mg/dl
3) 2-hour plasma glucose $\geq 200$ mg/dl during an OGTT
4) A1c $\geq 6.5$

Diabetes Care, 2012, 35, S11-63

Natural History of Type 1 Diabetes
Diabetes: “Catabolism Run Amok”

Patient J.L., December 15, 1922
February 15, 1923
Miracle of Insulin

What does insulin do?
Starting Insulin Doses: Based on age, body weight, and pubertal stage

<table>
<thead>
<tr>
<th>Toddlers/Pre-school</th>
<th>0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>School age/Pre-pubertal</td>
<td>0.5-0.75</td>
</tr>
<tr>
<td>Early puberty</td>
<td>0.75</td>
</tr>
</tbody>
</table>
| Pubertal | 1.0-1.5 (males)  
|           | 1.0-1.3 (females)  
|           | Rarely > 2.0 |
| DKA | 1.0-2.0 |

Time Action of Endogenous Insulin

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset of action</th>
<th>Peak of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular</td>
<td>30-60 min</td>
<td>2-4 h</td>
</tr>
<tr>
<td>NPH</td>
<td>1-2 h</td>
<td>4-8 h</td>
</tr>
<tr>
<td>Lispro/aspart</td>
<td>5-15 min</td>
<td>1-2 h</td>
</tr>
<tr>
<td>Glargine</td>
<td>1-2 h</td>
<td>Flat</td>
</tr>
</tbody>
</table>

Comparison of Human Insulins / Analogues
Insulin preparations

NPH + Novolog/Humalog/Regular (Mixed/Conventional/2 injections/day)

NPH + Humalog/Novolog (MDI or 3 Injections/day)
Lantus + Novolog/Humalog
(4 Injections/day: Basal-Bolus Poor man’s pump)

Insulin Pump Brands

Goals of Intensive Diabetes Management in Children

- Normal growth and development
- Age-appropriate glycemia
- Avoid short-term crisis
  - Hypoglycemia/Hyperglycemia
  - DKA
- Minimize long-term complications
Glycemic Control in Pediatrics

Diabetes Association targets the following goals:

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Pre-prandial Blood glucose (mg/dL)</th>
<th>Bedtime/overnight Blood glucose (mg/dL)</th>
<th>Hemoglobin A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6</td>
<td>100 - 180</td>
<td>110 - 200</td>
<td>&lt;8.5 (but &gt;7.5)</td>
</tr>
<tr>
<td>6-12</td>
<td>90 - 180</td>
<td>100 - 180</td>
<td>&lt;8</td>
</tr>
<tr>
<td>13-19</td>
<td>90 - 130</td>
<td>90 - 150</td>
<td>&lt;7.5</td>
</tr>
</tbody>
</table>

Diabetes Care 2009; 32: S13-S82.

Correlation of A1c with average glucose

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>Mean Blood Glucose (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>126</td>
</tr>
<tr>
<td>7</td>
<td>154</td>
</tr>
<tr>
<td>8</td>
<td>183</td>
</tr>
<tr>
<td>9</td>
<td>212</td>
</tr>
<tr>
<td>10</td>
<td>240</td>
</tr>
<tr>
<td>11</td>
<td>269</td>
</tr>
<tr>
<td>12</td>
<td>298</td>
</tr>
</tbody>
</table>

Diabetes Care, 2008, 31, 1473-1478
SEARCH Study

• Population-based, observational study of physician-diagnosed diabetes among youth <20 years of age
• Initiated in 2000
• Funded by CDC, NIH
• Collects data from 6 centers
  – 4 geographically based (Colorado, Ohio, South Carolina, Washington)
  – 2 health plan-based (California, Hawaii)


CDC=Centers for Disease Control and Prevention; NIH=National Institutes of Health
• 6379 youth with diabetes in a population of ~3.5 million
  – Average age at diagnosis: 8.4 years
  – Average duration of diabetes: 56 months (range, 38-60 months)
• Estimated prevalence of U.S. youth aged 0-19 years with diabetes in 2001
  1.82 cases per 1000 youth
  (95% CI: 1.78-1.87 per 1000 youth)
Cancer: 1.24 per 1000
Asthma: 120 per 1000


### Demographics, Prevalence

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of cases (%)</th>
<th>Population denominator, n (%)</th>
<th>Prevalence, cases per 1000 youth (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>6379</td>
<td>3,499,846</td>
<td>1.82 (1.78-1.87)</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4 y</td>
<td>255 (4.0)</td>
<td>829,589 (23.7)</td>
<td>0.31 (0.27-0.35)</td>
</tr>
<tr>
<td>5-9 y</td>
<td>1094 (17.2)</td>
<td>786,263 (22.0)</td>
<td>1.25 (1.18-1.32)</td>
</tr>
<tr>
<td>10-14 y</td>
<td>2100 (32.2)</td>
<td>925,426 (26.5)</td>
<td>2.29 (2.20-2.39)</td>
</tr>
<tr>
<td>15-19 y</td>
<td>2910 (45.6)</td>
<td>886,568 (24.8)</td>
<td>3.35 (3.23-3.47)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3156 (49.5)</td>
<td>1,787,208 (51.1)</td>
<td>1.77 (1.71-1.83)</td>
</tr>
<tr>
<td>Female</td>
<td>3223 (50.5)</td>
<td>1,712,638 (48.9)</td>
<td>1.86 (1.82-1.90)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHW</td>
<td>4382 (68.7)</td>
<td>2,025,426 (57.9)</td>
<td>1.26 (1.20-1.32)</td>
</tr>
<tr>
<td>Black</td>
<td>723 (11.3)</td>
<td>373,569 (10.6)</td>
<td>1.83 (1.76-1.88)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>826 (13.0)</td>
<td>641,414 (18.3)</td>
<td>1.09 (1.01-1.18)</td>
</tr>
<tr>
<td>API</td>
<td>257 (4.2)</td>
<td>325,403 (9.2)</td>
<td>0.79 (0.74-0.84)</td>
</tr>
<tr>
<td>AI</td>
<td>180 (2.8)</td>
<td>139,004 (4.0)</td>
<td>1.29 (1.12-1.50)</td>
</tr>
</tbody>
</table>

Characteristics of T1DM and T2DM

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Type 1 DM</th>
<th>Type 2 DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Female~Male</td>
<td>Female&gt;Male</td>
</tr>
<tr>
<td>Mean age at dx</td>
<td>10 years</td>
<td>13.5 years</td>
</tr>
<tr>
<td>Autoimmunity</td>
<td>Common (~85%)</td>
<td>Absent</td>
</tr>
<tr>
<td>Family Hx DM</td>
<td>5%</td>
<td>&gt;85%</td>
</tr>
<tr>
<td>Obesity (BMI&gt;85%)</td>
<td>~20%</td>
<td>95%</td>
</tr>
<tr>
<td>A. Nigricans</td>
<td>Uncommon</td>
<td>&gt;60%</td>
</tr>
<tr>
<td>Symptoms at Dx</td>
<td>Common (~90%)</td>
<td>Frequent (~50%)</td>
</tr>
<tr>
<td>DKA at Dx</td>
<td>Frequent (~30%)</td>
<td>Infrequent (&lt;10%)</td>
</tr>
</tbody>
</table>

Clinical features suggestive of T2DM in an obese child

• Evidence of insulin resistance
• Acanthosis nigricans
• Hypertension
• Dyslipidemia
• NASH
• Presentation during or soon after puberty
• T2DM in first-degree relative
• Sleep apnea
• Polycystic Ovarian Syndrome
• Unconventional presentation
• Candidiasis
• Dx on routine PE

Challenge #1: As youth with T1DM are more obese, the clinical distinction between T2DM and obese T1DM is difficult
Diabetes Presentation
No difference in sx except weight loss

Differences in signs not absolute

Adapted from Pediatrics, 1997

The Many Faces of Diabetes

Acanthosis nigricans

Non-hispanic white African-American
Diabetes autoimmune panel is needed to distinguish obese T1DM vs T2 DM

<table>
<thead>
<tr>
<th></th>
<th>Non-Hispanic White</th>
<th>African American</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>7.7%</td>
<td>10%</td>
</tr>
<tr>
<td>Islet Cell Ab (&lt; 5 u/ml)</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>Insulin antibody (&lt; 0.5 uU/ml)</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>GAD 65 Ab (&lt; 0.5 u/ml)</td>
<td>(-)</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Approach to the determination of new-onset DM in the obese adolescent

How do children with diabetes fare in terms of glycemic control?
Treatment Options for T2DM in Adolescents and Youth: TODAY Study

- NIH-sponsored multi-center clinical trial
- Screened >1200 kids age 10-17 years <2 years T2DM
- Enrollment started 2004 for 5 year follow-up
- 1088 DAA-negative subjects randomized to 3 arms:
  - Metformin alone
  - Metformin + Rosiglitazone
  - Metformin + intensive lifestyle intervention (↓7-10 %)

Primary outcome:
Loss of glycemic control, HbA1c > 8 % for 6 months or requiring insulin
Two drugs are better than one!

Failure rate after average f/u 3.86 yrs:
- Metformin alone: 51.7%
- Metformin + Rosiglitazone: 38.6%
- Metformin + lifestyle intervention: 46.6%

Glycemic control in diabetes? Why is it important?

To prevent acute and chronic complications.

Acute Complications
- Poor growth, delayed puberty, weight loss
- DKA: 1-3% mortality due to cerebral edema
- Hypoglycemia: neurocognitive deficits esp. in < 5 yrs of age
Mauriac syndrome
From Wikipedia, the free encyclopedia

Mauriac syndrome is a rare complication in children and adolescents with diabetes mellitus type 1, characterized by hepatomegaly, growth impairment, and cushingoid features. It can occur as a result of abnormal blood sugar levels and the symptoms tend to rectify with attainment of euglycemia (normal blood sugar levels).

References

Changes in Diabetes Management

The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long Term Complications in Insulin Dependent Diabetes Mellitus

The Diabetes Control and Complications Trial Research Group

NEJM 1993 Sep 30;329(14):977-86.
Diabetes Control and Complications Trial (DCCT)

Risks & Benefits of Intensive Diabetes Therapy (DCCT)

- Decreased Risk (%)
  - Progressive retinopathy 60
  - Microalbuminuria 40
  - Neuropathy 60

- Increased Risk (%)
  - Severe hypoglycemia 300

It’s not that easy!!
The future: Components of closed loop system

Sensor Augmented Pump Therapy
Conclusions:

• With discovery of insulin, DM changed from fatal disease to chronic disease
• Great strides in day to day mgmt
• Continue to struggle with challenges of normoglycemia.

Thank you for your attention.