Advances in Managing Diabetes in Youth

March 1, 2012
Diabetes in Youth: An Update

- The Problem
  - Increasing Incidence of Type 1 Diabetes
- The Cause
  - New Information on an Enterovirus connection
- New Therapy
  - Closed Loop Pump
- Best Treatment Until Cure
  - Proactive Team Approach
The Problem

Increasing Incidence of Type 1 Diabetes

- Incidence of DM is doubling every 20 years
- Disproportionate increase among young children
EURODIAB Study Group (2009)

- Examined 20 population-based registries across 17 countries in Europe
- Data from 1989 through 2003
- Ascertainment assessed to be > 90%
- Country to country variation in incidence, but all increasing (except Spain and Luxembourg)

Patterson, Lancet 2009, Vol 373, p 2027, 2009
Incidence and Increase in Incidence

Figure 2: Inverse association between rate of incidence increase and average incidence
Incidence rate on horizontal axis, plotted on a logarithmic scale. Spearman rank correlation coefficient $r_s=-0.52$, $p=0.02$.

Patterson, Lancet 2009, Vol 373, p 2027, 2009
Increased Incidence of Type 1 DM

- Overall: 3.9% per year increase in incidence
- 0-4yo: 5.4% per year increase
- 5-9yo: 4.3% per year increase
- 10-14yo: 2.9% per year increase

Patterson, Lancet 2009, Vol 373, p 2027, 2009
Why the increased incidence?

- “Modern Lifestyle”
  - increased weight and/or height
  - C-section deliveries
  - reduced frequency of early infections/exposures

- Lower incidence with larger increase over time in the Eastern European countries may support this

Patterson, Lancet 2009, Vol 373, p 2027, 2009
SEARCH Study (2009)

- Not population based. Rather, sampled data from US
- 0-19 yo
- Prevalence DM1 0.2% of all 0-19 yo non-Hispanic white youth
- Prevalence DM2 0.018% of all 10-19 yo non-Hispanic white youth
- Incidence DM1 23.6/100,000 (0-19)
- Incidence DM2 3.7/100,000 (10-19)
SEARCH Study (2009)

- Incidence DM1 appears to be rising in US, too.
- Data is restricted to 0-14yo:
  - SEARCH (2002-2005) 27.5
  - Allegheny (1990-1994) 17.8
  - Alabama (1990-1995) 14.6
  - Colorado (1978-1988) 16.4
Implications of this Increased Incidence

- More children with type 1 diabetes:
  - In Europe  Total
    - 2005: 94,000
    - 2020: 160,000

- AND, getting diabetes younger, so:
  - More dangerous presentation (cerebral edema, DKA)
  - More patient-years needed with Ped Endo
    - A 13 yo new onset will need 20 visits until 18yo
    - A 3 yo new onset will need 60 visits until 18 yo
  - More years of potential exposure to hyperglycemia
New Information on the Enterovirus Connection
New Information on Enterovirus connection

- Enterovirus can cause DM in mice
- Enterovirus can infect human β-cells in islet cell culture
- Enterovirus detected in apparently chronic infection of β-cells in some DM patients at autopsy
- Human monocyte-derived dendritic cells will phagocytose enterovirus-infected β-cells. These are antigen presenting cells.
Finnish Study (2011)

- Long term study of babies with high risk for DM identified by HLA risk genes.
- High risk babies screened for islet cell antibody positivity every 3-12 months.
- When a child developed DM1, a series of controls with same sex, birth month, HLA risk genes, and region of country were identified.
- RT-PCR was performed on previous serum samples for non-specific enteroviral RNA.
- n = 38 cases, 140 matched controls

Oikarinen, Diabetes, Vol 60, p 276, 2011
Finnish Study (2011)

![Graph showing the proportion of EV+ samples (%)]

- Birth-T1D: P=0.01
- Birth-before 6 month period prior Aab
- 6 month period prior Aab: P=0.004
- Aab-T1D

Oikarinen, Diabetes, Vol 60, p 276, 2011
Finnish Study (2011)

- Conclusion:
  - Enterovirus RNA is more likely to be present in serum in the 6 months before islet cell antibody positivity

- But serum enterovirus infection typically only lasts 2 weeks, so could miss it. Or, maybe there is chronic infection that triggers Ab positivity

- There are 100 types of enterovirus: polio, coxsackie A and B, echovirus. Which one: ?

Oikarinen, Diabetes, Vol 60, p 276, 2011
Norwegian Study (2011)

- Similar study, but looked for enterovirus in stool samples every month. No difference between cases and controls.

Tapia, Diabetes Care, Vol 34, p 151, 2011
DAISY Study (2011)

- Similar study in US, but patients already had positive antibodies.
- n=36
- Enterovirus was more likely to be detected in serum in the 4 months before progression from antibody positive to DM

<table>
<thead>
<tr>
<th>Type of sample</th>
<th>Person-years of follow-up</th>
<th>Cases progressing to type 1 diabetes in intervala</th>
<th>Unadjusted HR (95% CI)</th>
<th>HR (95% CI) adjusted for islet autoantibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No enterovirus RNA in previous sample</td>
<td>494</td>
<td>33</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>Enterovirus RNA in previous sample</td>
<td>6.5</td>
<td>3</td>
<td>6.36 (1.89–21.4)†</td>
<td>7.02 (1.95–25.3)</td>
</tr>
</tbody>
</table>

Not detected in stool before conversion to DM1

Stene, Diabetes, Vol 59, p 3174, 2010
Finnish Study (2012)

- Endoscopy biopsies of distal duodenum
  - 39 DM1 patient
  - 40 Celiac patients without DM1
  - 41 patients with neither DM1 nor Celiac

- Enterovirus detected by In Situ Hybridization to common enteroviral RNA, confirmed by RT-PCR

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Subjects positive for enterovirus RNA by ISH in small intestine biopsy samples</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All positive</td>
</tr>
<tr>
<td>T1D patients (N = 39)</td>
<td>29 (74)**</td>
</tr>
<tr>
<td>Celiac disease patients (N = 40)</td>
<td>18 (45)</td>
</tr>
<tr>
<td>Control subjects (N = 41)</td>
<td>12 (29)</td>
</tr>
</tbody>
</table>

Data are N (%). Weak positive, an average of 1–10 positive cells per field; moderate positive, 10–100 positive cells per field; strong positive, >100 cells per field. T1D, type 1 diabetic. **P < 0.001 compared with control subjects. *P = 0.035 compared with control subjects.

Oikarinen, Diabetes, Vol 61, p 687, 2012
Enteroviruses

- An intriguing target for prevention of type 1 DM
  - A vaccine to prevent would be the least expensive cure

- But: association does not prove causation

- Which enterovirus (there are 100 serotypes)

- How is enterovirus acting:
  - to expose antigen and start autoimmunity (Finnish study), or
  - to accelerate autoimmunity (US study)?
Closed Loop Pump
Closed Loop Pump

- Glucose sensor that inputs data to an
- Algorithm that regulates insulin delivery via an
- Insulin pump that physiologically disposes of
- Glucose . . . .
Insulin pumps

1977 “Biostator” IV

1960’s Prototype IV
Insulin pumps

1979 Sub Cu

1982 Wearable Sub Cu
Insulin pumps

Model 515

Model 715
Pump Therapy

Insulin to Cover the Meal

- Breakfast
- Lunch
- Dinner
- Snack

Basal

Combo
Bolus

Combo
Bolus

Bolus

Combo
Bolus

Bolus
Continuous Glucose Monitor (CGM)

Developed in 1999
Insulin Pump + CGM = Artificial Pancreas? 

- Currently “manual”:
  - Patient sees the glucose frequently and adjusts the pump
  - CGM also adds a new dimension of trend

125 Declining

125 Increasing
Why not automate/computerize this process?

- CGM Limitations
  - Senses glucose in interstitial fluid that runs 20 minutes behind blood glucose. No problem if blood glucose is stable, but not after a meal or after an insulin bolus
  - Sensor has processing time: can present BG only every 5-10 minutes
  - Sensors “drop out” intermittently
  - Sensor has limited accuracy at low BG
Why not automate/computerize this process?

- Insulin Limitations
  - Takes 20 minutes for pumped insulin to start working and 120 minutes to peak
  - Duration of up to 240 minutes
  - Liver is not preferentially insulinized, requiring hyperinsulinemia
  - Variable absorption from sub cu site
Does CGM improve glucose control?

- It alarms for highs and lows
- It provides real-time feedback of glucose values

- STAR3 trial (2010)
  - Basal bolus injection vs. Pump Augmented with CGM
STAR3 Trial: Pre-closed loop (2010)

- 7-70 yo with Type 1 DM with A1c 7.4 to 9.5%
- On basal bolus injection therapy and NOT on an insulin pump in the previous 3 years.
- n=552
- Randomized to
  - Injection therapy, or
  - Pump therapy with CGM. [Remember, the CGM did NOT control the pump]
- Endpoints
  - A1c
  - Hypoglycemia events

Bergenstal, NEJM Vol 363, p 311, July 2010
A1c Results in STAR3 trial

Bergenstal, NEJM Vol 363, p 311, July 2010
A1c Results in CGM users in STAR3

- By frequency of use of CGM

Bergenstal, NEJM Vol 363, p 311, July 2010
STAR3: Time spent hyper or hypo glycemic

<table>
<thead>
<tr>
<th></th>
<th>Sensor/ Pump</th>
<th>Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;250 mg/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline</td>
<td>9.99±9.63</td>
<td>10.62±9.64</td>
</tr>
<tr>
<td>At 1 yr</td>
<td>5.41±6.60</td>
<td>10.70±11.90</td>
</tr>
<tr>
<td>&gt;180 mg/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline</td>
<td>32.26±19.70</td>
<td>33.38±19.72</td>
</tr>
<tr>
<td>At 1 yr</td>
<td>20.36±15.73</td>
<td>32.23±23.41</td>
</tr>
<tr>
<td>&lt;70 mg/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline</td>
<td>0.27±0.50</td>
<td>0.29±0.48</td>
</tr>
<tr>
<td>At 1 yr</td>
<td>0.24±0.43</td>
<td>0.28±0.51</td>
</tr>
<tr>
<td>&lt;50 mg/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline</td>
<td>0.02±0.09</td>
<td>0.02±0.06</td>
</tr>
<tr>
<td>At 1 yr</td>
<td>0.02±0.05</td>
<td>0.02±0.08</td>
</tr>
</tbody>
</table>
STAR3 Adverse events

- No statistical difference between groups in
  - Severe Hypoglycemia rate
  - DKA rate

- BUT:
  - What was the effect of the pump vs. the CGM?
Steps toward Closing the Loop

- In research setting only, step by step:
  1) PID algorithm during 24 hours
  2) Fuzzy Logic/ MPC algorithm during night
  3) Hybrid control (Manual bolus, MPC basal), 24 h
  4) Truly automatic low glucose suspend

- Future:
  5) ? Conventional pump day, automatic night
  6) ? Automatic 24 hours
Yale Study (2008)

- 13-20 yo with DM1 over 1 yr and A1c <9% on insulin pumps.
- Closed loop: n= 8. The pump was adjusted with PID algorithm for 34 hours
- Hybrid closed loop: n=9. The patient gave half of a normal pre-meal bolus manually, then pump was adjusted with PID algorithm for 34 hours
- Outcome: mean and peak postprandial glucose levels
Yale Study (2008)

- PID control:
  - Proportional component
    - Proportional to elevation of BG
  - Integral component
    - Extra insulin if the proportional component not adequate to reduce BG
  - Derivative component
    - Extra insulin based on rate of increase of BG

Weinzimer, Diabetes Care, Vol 31, p 935, 2008
Yale Study (2008)

- Hybrid closed loop worked better than closed loop, but neither worked wonderfully

Weinzimer, Diabetes Care, Vol 31, p 935, 2008
Yale Study (2008)

- Glucose sensor tends to be delayed (A)
- Insulin appearance in plasma is delayed (B)
Need to use predictive algorithm

- Yale study and others that use PID algorithm will be unable to be fast enough to prevent BG spikes
- They rely on mathematical calculations based on past data, not predictions of what will happen in future
- MPC algorithm uses prediction of glucose dynamics and the patient metabolic system coupled with brakes built into the system to avoid over aggressive insulin

Weinzimer, Diabetes Care, Vol 31, p 935, 2008
Cambridge Study (2011)

- Use of MCP algorithm
- Computer controlled administration of insulin based on blood glucose when not actively eating.

Hovorka, BMJ 2011; 342:d1855
doi:10.1136/bmj.d1855
Cambridge Study: Overnight closed loop

- Subjects: 18-65 yo with DM1 on pump for >3m
- n=24
- Each subject studied for two nights in random cross over design:
  - conventional insulin pump settings
  - computer adjusted pump settings based on sensor data: closed loop
- Two scenarios: after a modest “eating in” 60g carb dinner and after an “eating out” 100g plus 500 ml wine dinner.

Hovorka, BMJ 2011; 342;d1855
doi:10.1136/bmj.d1855
Cambridge Study

- **Algorithm**
  - Every 15 minutes, research nurse inputted the CGM reading into the computer
  - Algorithm essentially forecasted the glucose in the medium term future and determined how the basal rate should be altered for the next 15 minute period.
  - The model aimed to maintain glucose between 104 and 131 mg/dl.
  - Nurse manually adjusted the pump according to computer algorithm.

Hovorka, BMJ 2011; 342;d1855
doi:10.1136/bmj.d1855
Cambridge study

- “Eating In”

Blue: Closed Loop Pump
Red: Standard Pump
Shading is quartiles

Computer algorithm starts
Cambridge study

- “Eating Out”

![Graph showing plasma glucose concentration and insulin infusion with labels for closed loop and standard pump, and quartile shading.]

Blue: Closed Loop Pump
Red: Standard Pump
Shading is quartiles
Cambridge study

Table 2 | Time plasma glucose level in target during closed loop delivery of insulin and conventional insulin pump therapy in two meal scenarios. Values are medians (interquartile ranges) unless stated otherwise

<table>
<thead>
<tr>
<th>Meal scenarios</th>
<th>Time (%) when plasma glucose in target range*</th>
<th>Paired difference† (%) (n=12)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Closed loop (n=12)</td>
<td>Insulin pump (n=12)</td>
<td></td>
</tr>
<tr>
<td>Eating in‡</td>
<td>80 (60 to 94)</td>
<td>51 (39 to 75)</td>
<td>15 (3 to 35)</td>
</tr>
<tr>
<td>Eating out§</td>
<td>70 (60 to 86)</td>
<td>47 (28 to 66)</td>
<td>28 (2 to 39)</td>
</tr>
</tbody>
</table>

Hovorka, BMJ 2011; 342;d1855
doi:10.1136/bmj.d1855
Cambridge study #2 (2011)

- Hybrid Closed Loop in Pregnant Women 24 hr
- n=12
- Compared 24 hour on conventional pump with 24 hour when MPC controlled the basal
- Included three 20 min walks and two brisk 50 min treadmill walks
- Not a lot of detail, but 81% of time in target BG range on pump and on hybrid closed loop
- Fewer episodes of symptomatic hypoglycemia on hybrid closed loop, but somewhat more time hyperglycemic.

Murphy, Diabetes Care Vol 34, p 2527, 2011
Medtronic Study (2012)

- Fully automatic, but still “in lab” study, of Low Glucose Suspend (LGS): pump shuts down for two hours after CGM signals BG <70 mg/dl.
- 17-58 yo with DM1 >1yr using insulin pump > 3m
- N=50
- Random crossover trial of normal pump and LGS-enabled pump on two separate days:
  - Overnight fast
  - AM exercise to BG <85
  - Monitor BG until 70, then continue to monitor for 4 hr
Medtronic Study

- A representative patient

**FIG. 1.** Data from one subject’s successful (A) low glucose suspend-On and (B) low glucose suspend-Off sessions: YSI (reference) plasma glucose values (red dots) and sensor glucose values (blue lines). The red line at 70 mg/dL represents the pump suspension triggering threshold in the low glucose suspend-On session, the green lines represent the beginning and ending of the 4-h observation period, and the blue rectangle in (A) represents the 2-h pump suspension.

Garg, Diabetes Technology and Therapeutics, Vol 14, p 1, 2012
Medtronic Study

- Aggregate data for all 50 subjects

"Mean duration of BG<70 was 32 min shorter"

Garg, Diabetes Technology and Therapeutics, Vol 14, p 1, 2012
Home Closed Loop Pump

- Will have a MPC-type algorithm
- Likely will require a priming (manual) bolus before meals and snacks
- May need to have more reliable CGM. Some studies use two CGM.
- May need to deliver insulin intraperitoneal
- May need to have intravenous glucose sensor
- May need to include glucagon before it can be aggressive enough without risk of hypoglycemia
- No trials yet of fully automatic closed loop
- Will still be a while until available
Home Closed Loop Pump

- No clinical trials at this time
- Cambridge has proposed, but not yet opened, a trial of conventional pump during day and closed loop at night.
Proactive Team Approach

- Until there is a cure (or an artificial pancreas) we need to ensure excellent diabetes care for our patients
Diabetes Care

- Happens in peoples homes, school, places of work; not in medical facility by medical personnel
- Medical aspects of diabetes care are relatively straightforward
- Psychosocial aspects are the biggest barrier to good diabetes care
The Job of the Diabetes Center

- Provide education on rationale for diabetes care
- Provide education on mechanics of diabetes care
- For pediatrics, provide ongoing re-education shifting from parent-focus to child-focus
At Nationwide Childrens Diabetes Center

- Initial Education:
  - 36-48 hours in hospital
    - Rationale for diabetes care
    - Mechanics of diabetes care
    - Role modeling behavior with each aspect of care
    - Docs, 6AW nurses, CDE, Dietitian, Social Worker, Rec Therapist
  - Follow up outpatient education in 1 week with CDE and RD
  - Follow up group class 2 weeks later with CDE, RD
  - Follow up in clinic 2 weeks later with Advanced Practitioner, SW
At Nationwide Childrens Diabetes Center

- **Ongoing Education:**
  - **Proactive approach**
    - Try to anticipate needs before disaster strikes
    - See CDE at least twice per year
      - Assesses skills and knowledge of parents (and child)
      - Re-education according to situation
      - Anticipatory guidance: what might be coming up in next year
        - Pump, school entry, driving, transition to adult endo
  - **See RD at least once per year**
    - Assess skills and knowledge of parents (and child)
    - Re-education according to situation
    - Anticipatory guidance: what might be coming up in next years
      - Pump, school meals, eating out, eating home cooked meals at grandma’s
At Nationwide Childrens Diabetes Center

- Ongoing Education:
  - Proactive approach
    - Try to anticipate needs before disaster strikes
    - See SW at least once per year
      - Assess family functioning and learning styles, literacy, child’s adjustment to diabetes, child’s and family’s motivations and readiness for diabetes care, who is doing which aspect of diabetes care, depression in patient or family, medical illness in family members, financial needs, other barriers to good diabetes care
      - Address needs: either in clinic or referrals in community
      - Anticipatory guidance: what might be coming up in next years
        - School change, insurance change, teen angst, bullying, sex, role modeling positive interactions with peers
Important things that we are working on

- Depression Screening

- Promote self-management, not dependence
  - We have a tendency to say, “just call us”
  - Too many patients come to clinic with beautifully documented blood glucoses all in 200s.

- Transition of care from Pediatric to Adult Endo
  - We lose a bunch of teens

- Benchmarking and sharing strategies with other programs
Number of DM1 Patients by Age
Number of DM1 Patients by Age

N=637 lost patients to 21 yo
Important things that we are working on

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Important things that we are working on

- Motivational Interviewing
  - “What part of living with diabetes is most difficulty right now?”
  - “How does this make you feel?”
  - “What things could you do to make it better?”
  - “Is there one thing that you will do between now and next visit?”
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- Best Treatment Until Cure
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