Youth-onset type 2 diabetes

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LEST WE THINK THIS IS NOT AN IMPORTANT PROBLEM

Yes!

Is Type 2 diabetes the same in kids as in adults?

And No!
Glucose Homeostasis

- Balance Between Insulin action and secretion
- Diabetes occurs when this balance is lost

![Diagram showing balance between insulin action and secretion]

Relationship Between Insulin Sensitivity and Insulin Response in Apparently Healthy Subjects

![Graph showing relationship between insulin sensitivity and insulin response]


The relationship between insulin secretion and insulin action during the development of T2D

![Graph showing relationship between insulin secretion and insulin action during T2D development]

Disposition index in NGT vs IGT vs T2D

- NGT: 3.38
- IGT: 1.92
- T2D: 0.58

p<0.001

From Bacha et al Diabetes Care 32: 100, 2009

Unique aspects of type 2 in US youth

US T2D Epidemiology: Adults versus Kids

<table>
<thead>
<tr>
<th></th>
<th>ADULTS</th>
<th>YOUTH (≤19 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence (new cases/yr)</td>
<td>~1,469,000 per year</td>
<td>~5,100 per year</td>
</tr>
<tr>
<td>Prevalence Overall</td>
<td>12.3 per 100 (12.3%)</td>
<td>0.5 per 1,000 (~1 in 200 obese)</td>
</tr>
<tr>
<td>10 - ≤14 years</td>
<td>12.3 per 100 (12.3%)</td>
<td>0.5 per 1,000 (~1 in 200 obese)</td>
</tr>
<tr>
<td>15 - ≤24 years</td>
<td>4.1 per 100 (4.1%)</td>
<td>0.23 per 1,000 (0.023%)</td>
</tr>
<tr>
<td>25 - ≤34 years</td>
<td>16.2 per 100 (16.2%)</td>
<td>0.00 per 1,000 (0.000%)</td>
</tr>
<tr>
<td>45 - ≤64 years</td>
<td>25.5 per 100 (25.5%)</td>
<td></td>
</tr>
<tr>
<td>65 and older</td>
<td>0.5 per 1,000 (0.05%)</td>
<td></td>
</tr>
<tr>
<td>Prevalence by Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13.8 per 100 (13.8%)</td>
<td>0.25 per 1,000 (0.025%)</td>
</tr>
<tr>
<td>Female</td>
<td>11.2 per 100 (11.2%)</td>
<td>0.50 per 1,000 (0.050%)</td>
</tr>
</tbody>
</table>
Type 2 Diabetes increases dramatically at puberty

Demographics and socioeconomic status of youth-onset T2D in the US

<table>
<thead>
<tr>
<th>Age</th>
<th>14.0 (12,16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of DM (months)</td>
<td>5 (4,8)</td>
</tr>
<tr>
<td>BMI Z-score</td>
<td>2.21 (1.89, 2.47)</td>
</tr>
<tr>
<td>Tanner 4/5</td>
<td>83.9%</td>
</tr>
<tr>
<td>Female</td>
<td>84.9%</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>19.9%</td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
</tr>
<tr>
<td></td>
<td>AA</td>
</tr>
<tr>
<td></td>
<td>AI</td>
</tr>
<tr>
<td>FH diabetes</td>
<td>59.6%</td>
</tr>
<tr>
<td>Nuclear</td>
<td>89.4%</td>
</tr>
<tr>
<td>GDM</td>
<td>33.3%</td>
</tr>
</tbody>
</table>

Lives with
- Both parents: 38.7%
- Mother: 47.0%
- Father: 5.1%
- Neither: 9.2%

Parental Education
- HS or less: 26.3%
- College or more: 16.8%

Income
- < 25k: 41.4%
- > 50k: 24.9%

Fasting glucose
- < 5.5: 93.4% (SD 6.7)
- 5.5-6.0: 84.0% (SD 5.5)
- 6.1-6.9: 14.7% (SD 6.7)
- ≥ 7.0: 0.1% (SD 0.4)

Healthy, Diabetes Care 2006

The prevalence of undiagnosed diabetes is low

<table>
<thead>
<tr>
<th>Measurement</th>
<th>6th grade N = 6367</th>
<th>8th grade N = 1740</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>≤ 85</td>
<td>22.4 (5.7)</td>
<td>24.3 (5.9)</td>
</tr>
<tr>
<td>85-94</td>
<td>50.5%</td>
<td>51.0%</td>
</tr>
<tr>
<td>≥ 95</td>
<td>19.8%</td>
<td>19.8%</td>
</tr>
<tr>
<td>BMI percentile (adjusted for age and gender)</td>
<td>29.7%</td>
<td>29.2%</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>93.4 (6.7)</td>
<td>98.2 (8.5)</td>
</tr>
<tr>
<td>&lt; 5.5</td>
<td>84.0%</td>
<td>59.5%</td>
</tr>
<tr>
<td>5.5-6.0</td>
<td>14.7%</td>
<td>34.3%</td>
</tr>
<tr>
<td>≥ 6.1-6.9</td>
<td>1.2%</td>
<td>5.8%</td>
</tr>
<tr>
<td>Fasting insulin (µU/mL) ≤ 30</td>
<td>6.2%</td>
<td>36.2%</td>
</tr>
</tbody>
</table>

*n=6 of which only 1 confirmed on follow-up testing; **n=7
Prevalence in youth much less than in adults
- Gender disparity present in adolescents that is not seen in adults
- Tightly linked to physiologic changes of puberty
- Disproportionate exposure to gestational diabetes
- Higher rate of spontaneous improvement
- More racially and socioeconomically challenged than adult type 2 populations
- Also
  - High prevalence of fatty liver
  - High prevalence of renal hyper-filtration
What have we known about the use of oral agents in pediatric type 2 diabetes

Evidence base prior to the TODAY study

- Metformin – FDA approved based on adult efficacy and a single highly flawed study
- Sulfonylurea (glimepiride) – a single study showing no superior efficacy to metformin and increased hypoglycemia and weight gain
- Rosiglitazone – never published
- 15+ pharmaceutical trials underway with slow recruitment


Treatment Options for Type 2 Diabetes in Adolescents and Youth

Funded by National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY)

Hypothesis: early initiation of combination therapy to reduce insulin resistance during puberty will be beneficial in youth with type 2 diabetes

Compared three treatment regimens on time loss of glycemic control
- Metformin
- Metformin + rosiglitazone
- Metformin + intensive lifestyle

Outcome – time to loss of glycemic control
- HbA1c ≥ 8.0% for 6 months or end-of-study HbA1c ≥ 10%
- Inability to wean from temporary insulin therapy due to metabolic decompensation (forced wean by algorithm)

Time to loss of glycemic control

Glycemic control in adults
Insulin Sensitivity and β-cell Function in TODAY

**Insulin Sensitivity**

- **A**
  - Title: [Insulin Sensitivity Oral Disposition Index](Kahn et al N Engl J Med 2006)
  - Diagram showing data points and lines indicating trends over time.

**Oral Disposition Index**

- **C**
  - Title: [β-cell function in adults](Pan et al, J Physio 2005)
  - Diagram showing data points and lines indicating trends over time.
What else have we learned from the TODAY study?

- At least 10% of youth clinically diagnosed with type 2 in reality have type 1.
- Hypertension, dyslipidemia, and microalbuminuria are prevalent at diagnosis and increase steadily over the first 6 years of T2D in youth. Retinopathy is uncommon.
- Exposure to gestational diabetes is a strong determinant of outcome.
- Physical activity levels in youth with T2D are lower than obese youth in NHANES.
- Depression and eating disorders are prevalent, but not more than in obese youth without diabetes.

Initial treatment with metformin was usually successful – even for participants on insulin.
Initial metformin therapy

- Of the 927 participants who entered run-in
  - 38% were being treated with insulin at screening
  - 90.9% achieved an HbA1c of < 8% on metformin alone
  - All but 11% could be weaned off of insulin
- HbA1c at the end of run-in was not related to insulin use at screening

![Graph showing HbA1c (%)

Screening vs End of run-in

Not on insulin at screening
On insulin at screening

Laffel et al. Pediatr Diabetes 2012
Kelsey et al Pediatr Diabetes 2016

Initial therapy in youth-onset T2D

Despite the evidence from TODAY that metformin will be inadequate for maintenance of glycemic control in 50% of youth...

- The majority of youth will attain an HbA1c in the non-diabetic range with initial metformin therapy
- Being on insulin at the start of metformin therapy is not related to failure to attain non-diabetic HbA1c
- Therefore, most youth with T2D on insulin can be weaned off insulin when metformin is started and achieve current HbA1c targets

Laffel et al. Pediatr Diabetes 2012
Kelsey et al Pediatr Diabetes 2015

Youth who cannot quickly achieve HbA1c in the non-diabetes range on metformin are likely to require insulin
Compared 2 groups
1. No loss of glycemic control before 48 months
2. Loss of glycemic control before 48 months

Performed multivariate analysis: baseline HbA1c and insulinogenic index were only factors related to likelihood of not failing by 48 months

HbA1c is more standard and clinically accessible

Does baseline HbA1c distinguish between those who will have durable control and those who will not?

After an initial course of metformin monotherapy with a target of < 8%, there is a difference in the distribution of HbA1c at baseline between Group 1 and Group 2.
Gender and race/ethnicity differences in positive likelihood ratio for HbA1c

Predictors of durability of metformin monotherapy in youth-onset T2D

- Youth who did not attain a non-diabetes range HbA1c after an average of 3 months on metformin monotherapy had a 4-fold increased likelihood of losing glycemic control prior to 48 months, with a median time to failure of 11 months
- HbA1c at the end of a relatively short period of metformin monotherapy may be a predictor of the need for additional therapy in youth-onset T2D

Weight loss is associated with improved glycemic and non-glycemic measures
**Weight Loss in TODAY**

- Addition of lifestyle intervention to metformin did not reduce loss of glycemic control:
  - 31% in met+lifestyle reduced % overweight by ≥7% at 6 months
    - Significantly different from met+rosi (17%)
    - Not different from met alone (24%)
  - Significant difference in reduction in % overweight between arms disappeared over 2 years as an increased percentage of those in other arms lost ≥7% of overweight.

**Was weight loss itself associated with benefits?**

Loss of ≥7% in % overweight significantly associated with improvements over first 2 years of TODAY:

- Lower HbA1c
- Lower cholesterol
- Lower LDL
- Higher HDL
- Lower TG
- Higher oDI

**Weight Loss in Youth-Onset T2D**

- Weight loss, no matter how achieved:
  - Lowers HbA1c
  - Improves cardiovascular risk markers
  - Improves β-cell function
- Despite the finding that an intensive lifestyle intervention was not able to achieve weight loss sufficient to alter the glycemic course in this demographic above and beyond metformin alone, weight loss remains an important goal in treatment of youth-onset T2D.
In light of TODAY, what should the approach to therapy be?

New Onset Diabetes in Overweight Youth

- A1c < 8.5%
  - No Acidosis with or without ketosis
  - Metformin PO bid
  - Titrate up to 2000 mg per day as tolerated

- A1c > 8.5%
  - Acidosis and/or DKA and/or HHNK
  - Basal insulin: start at 0.5 U/kg/day and escalate every 2-3 days based on meter glucose readings
  - Manage DKA or HHNK IV insulin until acidosis resolves, then subcutaneous

Pancreatic autoantibodies
- Continue metformin
- Wean insulin
- A1C Goals Not Met
  - Initiate or continue add-on insulin therapy - basal insulin to max 1.5 unit/kg/day
  - Continue or initiate MDI insulin therapy

Keep in mind
- Metformin was effective in attaining glycemic control in >90% of participants entering TODAY screening, irrespective of the current medications
- Metformin was effective in maintaining durable control in ~50% of participants in TODAY
- Metformin has numerous beneficial effects, is inexpensive and well-tolerated
- Therefore, metformin remains an excellent choice for initial monotherapy in T2D
Determinants of Control

- Baseline A1c is the primary predictor of likelihood of loss of glycemic control
- The primary determinant of baseline A1c in youth in TODAY was β-cell function
- Therefore, β-cell function is the key target for therapy for maintenance of glycemic control

Implications for management

- B-cell loss in adolescents with T2D is progressive and rapid
- Loss of β-cell function is the primary predictor of failure to maintain glycemic control
- Therefore, add-on therapy needs to address the deterioration of insulin secretion
- ORIGIN, and others, demonstrate that treat-to-target (A1c of 6.5% or FPG < 95ng/dL or 5.3 mmol/L) is more effective than step-wise treat-to-failure in maintaining target at 5 years
- Therefore, we want to select add-on therapy that will get the patient to target and keep him/her there

Options

- Sulfonylurea (1 published study – not superior to metformin)
  - Hypoglycemia, β-cell failure
- GLP-1 analogs (no pediatric studies)
- DPP-4 inhibitors (no pediatric studies)
- TZD (no pediatric studies)
- Glinides (no pediatric studies)
- Acarbose (no pediatric studies)
- Colesevelam (no pediatric studies)
- SGLT-2 Inhibitors (no pediatric studies)
- Bromocriptine (no pediatric studies)
- Insulin
Why are so few drugs approved for youth-onset T2D?

Requirements and waivers for pediatric evaluation

FDA and PREA
Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) of 2007, all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

EMA and PIP (pediatric investigation plan)
A development plan aimed at ensuring that the necessary data are obtained to support the authorisation of a medicine for children, through studies in children.

Waivers have been granted by the FDA and EMA:
- Does not provide any meaningful therapeutic benefits
- "Unsafe in all pediatric age groups..."
- "Not likely to be used..."

Too many studies

<table>
<thead>
<tr>
<th>MOA Class</th>
<th>Drug Name</th>
<th>FDA Approval</th>
<th>Clinical Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonlyurea</td>
<td>Glyburide</td>
<td>1984, May</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Glipizide</td>
<td>1984, May</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Glimepiride</td>
<td>1995, November</td>
<td>Included in USPI Gottschalk et al. 2007</td>
</tr>
<tr>
<td>Biguanide</td>
<td>Metformin</td>
<td>1995, March</td>
<td>Yes, 2000, December</td>
</tr>
<tr>
<td>Alpha glucosidase</td>
<td>Acarbose</td>
<td>1995, September</td>
<td>No</td>
</tr>
<tr>
<td>Meglitinide</td>
<td>Repaglinide</td>
<td>1997, December</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Nateglinide</td>
<td>2000, December</td>
<td>No</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>Rosiglitazone</td>
<td>1999, May</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Pioglitazone</td>
<td>1999, July</td>
<td>Small; not published</td>
</tr>
<tr>
<td>Amylin analogue</td>
<td>Pramlintide</td>
<td>2005, March</td>
<td>No</td>
</tr>
<tr>
<td>GLP-1 analogue</td>
<td>Exenatide</td>
<td>2005, April</td>
<td>S/E study ongoing</td>
</tr>
<tr>
<td></td>
<td>Liraglutide</td>
<td>2010, January</td>
<td>S/E study ongoing</td>
</tr>
<tr>
<td></td>
<td>Exenatide LAR</td>
<td>2012, January</td>
<td>S/E study ongoing</td>
</tr>
<tr>
<td></td>
<td>Dulaglutide</td>
<td>2014, May</td>
<td>S/E study ongoing</td>
</tr>
<tr>
<td></td>
<td>Sitagliptin</td>
<td>2006, October</td>
<td>S/E study ongoing</td>
</tr>
<tr>
<td></td>
<td>Saxagliptin</td>
<td>2009, July</td>
<td>S/E study ongoing</td>
</tr>
<tr>
<td></td>
<td>Linagliptin</td>
<td>2011, May</td>
<td>S/E study ongoing</td>
</tr>
<tr>
<td></td>
<td>Alogliptin</td>
<td>2013, January</td>
<td>S/E study ongoing</td>
</tr>
<tr>
<td>Bile acid sequestrant</td>
<td>Colesevelam</td>
<td>2009, October (diabetes)</td>
<td>No</td>
</tr>
<tr>
<td>SGLT-2 inhibitor</td>
<td>Canagliflozin</td>
<td>2013, March</td>
<td>S/E study pending</td>
</tr>
<tr>
<td></td>
<td>Dapagliflozin</td>
<td>2014, January</td>
<td>S/E study ongoing</td>
</tr>
<tr>
<td></td>
<td>Empagliflozin</td>
<td>2014, August</td>
<td>S/E study ongoing</td>
</tr>
<tr>
<td>Dopamine agonist</td>
<td>Bromocriptine</td>
<td>2009, May (diabetes)</td>
<td>No</td>
</tr>
</tbody>
</table>

FDA and Clinicaltrials.gov web sites.

Too many studies
Too Few Patients

- > 5,000 patients aged 10-17 years required to complete current and planned FDA mandated clinical trials
  - Prevalence of T2D in youth <16 years of age in the USA: < 25,000 – 40,000
  - 12-15% of all existing pediatric age type 2 diabetes patients in the US
- EMA has additional mandated studies, requiring > 30% "European" participants
  - Prevalence of youth-onset T2D in Europe not well known, but clearly lower than the US

Challenges of doing clinical trials in youth-onset T2D?

- Target population demographics:
  - Widely dispersed
  - Poverty
  - Low family educational attainment
  - Social challenges
  - Limited access to healthcare
- Challenging distinction between type 1 and type 2
- Study design challenges
  - A1C inclusion ranges (HbA1c 7-10%)
  - Exclusions (fatty liver, two parent consent)
  - Frequent, fasting visits

Adverse Impact of Eligibility Criteria on Pool of Potential Subjects

<table>
<thead>
<tr>
<th>Eligibility Criteria</th>
<th>PDC subjects eligible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug naïve + A1c &gt; 7.0%</td>
<td>7%</td>
</tr>
<tr>
<td>Metformin + A1c &gt; 7.0%</td>
<td>6%</td>
</tr>
<tr>
<td>Met + Insulin + A1c &gt; 7.0%</td>
<td>56%</td>
</tr>
</tbody>
</table>
At diagnosis:

- Lifestyle + Metformin
- Lifestyle + Metformin + Basal insulin

For patients with HbA1c >6.5%, the following may be considered:

- GLP-1 agonist
- SGLT2 inhibitor
- Metformin intolerance

If the patient remains uncontrolled, combination therapy or bariatric surgery may be considered.
Adverse events

- 6 of 30 TeenLabs participants (20%) experienced complications requiring reoperation and/or readmission
- 6 of 30 TeenLabs participants (20%) required subsequent hospitalization for observation or other interventions (non-abdominal operations)
- 23% (2/63) of TODAY participants required hospital admission during the 2 year period

To be covered at Afternoon Case Workshop

- Approach to prediabetes
- Distinguishing type 1 and type 2 diabetes
- Management of comorbidities
- Whatever else comes up
  - Management of the obese adolescent with type 1 diabetes
  - Monogenic diabetes

Thank you for your attention