Type 2 Diabetes Mellitus in Adolescents

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Yes!

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

And No!
Unique aspects of type 2 in US youth
**Current Incidence of T2D in Adolescents**

- **SEARCH for Diabetes in Youth**
  - rare in children younger than 10 years of age, regardless of race or ethnicity.
  - after 10 years of age, newly diagnosed cases
    - 14.9% in non-Hispanic whites (NHW)
      - 0.19 cases per 1000 NHW youth
    - 46.1% in Hispanic youth
    - 57.8% in non-Hispanic Blacks (NHB)
    - 69.7% in Asian/Pacific Islanders
    - 86.2% in American Indian (AI)
      - 1.74 cases per 1000 AI youth
  - In total, approximately **3700** youth under 20 years of age are diagnosed with T2D in the US annually

The prevalence of undiagnosed diabetes is low

- **NHANES 1999-2000** – 915 12-19 years
  - DM based on fasting criteria < 1%

- **STOPP-T2D**
  - 1750 8th graders, BMI > 85%ile
    - 0.4% - DM – fasting criteria
    - 0.1% - DM - OGTT
    - 2% with IGT

Unique Aspects of Studying T2D in Youth

- Prevalent obesity, diabetes, and insulin resistance
- Poor diabetes control, diet, and lifestyle
- Increased family health burden
  - Diabetes and non-diabetes related medical disorders
  - Psychological and psychiatric disorders
- Frequent family dysfunction
  - Unstable residence and transportation
  - Contact with legal system
  - School absences or dropouts
  - Poor communication
  - Poor parenting
  - Domestic violence
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
Primary Aim

To compare three treatment regimens on time to failure (loss of glycemic control)

- Metformin
- Metformin + rosiglitazone
- Metformin + intensive lifestyle
RCT Study Design

- 2-6 month pre-randomization run-in period
  - provide standard diabetes education
  - wean off all other diabetes medications
  - on metformin (max 1000 mg bid, min 500 mg bid)
  - assess ability to adhere to protocol
  - HbA1c < 8.0%
- 3 treatment arms
- 4 year rolling enrollment period
- 2-6 years follow-up
Major Inclusion Criteria

- Age 10 to 17 years
- Diabetes diagnosed by ADA criteria
- Duration of diabetes < 2 years
- BMI ≥ 85th percentile at diagnosis
- Absence of pancreatic autoimmunity
- Fasting C-peptide > 0.6 mmol/L
Primary Outcome: Treatment Failure

- HbA1c $\geq 8.0\%$ for at least 165 days (5½ months) or ended TODAY $\geq 10\%$.

- Inability to wean from temporary insulin therapy due to metabolic decompensation (forced wean by algorithm).

An adjudication group of three external experts determined reasons for and dates of PO in every case.
CONSORT Diagram

Screening
N = 1211

Run-in
N = 927 (76.5%)

Randomization
N = 699 (58.1%)

Exclusions: n = 284
- Positive antibodies 116 (9.6%)
- C-peptide < 0.6 14 (1.1%)
- Transaminase > 2.5 ULN 17 (1.4%)
- Other 137 (11.3%)

Exclusions: n = 228
- Inability to maintain A1c < 8% 74 (8.0%)
- Transaminase > 2.5 ULN 3 (0.3%)
- Inability to complete run-in 89 (9.6%)
- Other 57 (6.1%)
What have we learned about the Cohort so far?

AUTOANTIBODY POSITIVITY IN SUBJECTS SCREENED FOR PARTICIPATION IN A TREATMENT TRIAL FOR T2D IN YOUTH

Klingensmith et al
Diabetes Care 33:1970-5
2010
All individuals screened for the TODAY study were considered by their pediatric endocrinologist to have T2D

- Participants were prescreened locally for autoantibodies at some sites
- Positive individuals may have been excluded from screening in TODAY
Results

Of the 1206 children screened, 119 (9.8%) were positive for diabetes autoimmunity

- 29 (2.4%) had only GAD
- 43 (3.6%) had only IA2
- 47 (3.9%) had both autoantibodies
# Antibody Negative vs. Positive Subjects

<table>
<thead>
<tr>
<th></th>
<th>Antibody negative (N=1092)</th>
<th>Antibody positive (N=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>14.0 (9, 17)</td>
<td>13.0 (10, 17)</td>
</tr>
<tr>
<td>Years since diagnosis</td>
<td>0.2 (0, 2.7)</td>
<td>0.2 (0, 6.5)</td>
</tr>
<tr>
<td>BMI Z-score**</td>
<td>2.3 (-0.3, 3.2)</td>
<td>1.9 (0.5, 2.9)</td>
</tr>
<tr>
<td>C-peptide**</td>
<td>3.8 (0, 19.3)</td>
<td>2.0 (0, 8.7)</td>
</tr>
<tr>
<td>HbA1c*</td>
<td>6.9 (4.5, 17.4)</td>
<td>7.6 (4.8, 19.9)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>156 (62, 873)</td>
<td>151 (85, 266)</td>
</tr>
<tr>
<td>Triglycerides**</td>
<td>106.5 (27, 9688)</td>
<td>77.0 (14, 948)</td>
</tr>
<tr>
<td>HDL**</td>
<td>39.0 (10, 95)</td>
<td>43.0 (25, 78)</td>
</tr>
<tr>
<td>LDL</td>
<td>92.0 (21, 449)</td>
<td>87.0 (22, 166)</td>
</tr>
<tr>
<td>SBP**</td>
<td>115.0 (84, 184)</td>
<td>110.7 (86, 144)</td>
</tr>
<tr>
<td>DBP**</td>
<td>68.3 (43, 109)</td>
<td>64.7 (44, 90)</td>
</tr>
</tbody>
</table>

*p < 0.05  
**P < 0.005  

Median (min, max)
**Antibody Negative vs. Positive Subjects**

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<tr>
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<th>Antibody negative (N=1092)</th>
<th>Antibody positive (N=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% female*</td>
<td>64.3</td>
<td>48.7</td>
</tr>
<tr>
<td>% non-white**</td>
<td>81.0</td>
<td>59.7</td>
</tr>
<tr>
<td>% insulin use*</td>
<td>38.6</td>
<td>53.8</td>
</tr>
<tr>
<td>% mother with diabetes**</td>
<td>40.0</td>
<td>21.0</td>
</tr>
<tr>
<td>% father with diabetes*</td>
<td>22.7</td>
<td>15.1</td>
</tr>
<tr>
<td>% with acanthosis**</td>
<td>83.1</td>
<td>68.1</td>
</tr>
</tbody>
</table>

* p<0.05

** P < 0.005

Klingensmith et al  
Diabetes Care 33:1970-5, 2010
9.8% of youth identified with T2D by pediatric endocrinologists on clinical grounds are antibody positive
- 7.5% have single high-titer or double positive antibodies

This may be a conservative estimate
- some potential subjects were prescreened for DAA
- insulin auto-antibodies were not measured
- anti ZnT8 (and other unknown antibodies were not measured)

Antibody positive youth have clinical features of type 2 diabetes that individually are indistinguishable from antibody negative youth
What have we learned about the Cohort so far?

CHILDREN AND ADOLESCENTS WITH TYPE 2 DIABETES: CHARACTERISTICS OF THE TODAY STUDY PARTICIPANTS AT BASELINE

The Today Study Group
J Clin Endocrinol Metab 96:159-67, 2010
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>14.0 ± 2.0</td>
</tr>
<tr>
<td>Duration of T2D (months)</td>
<td>7.8 ± 0.44</td>
</tr>
<tr>
<td>BMI</td>
<td>34.9 ± 7.6</td>
</tr>
<tr>
<td>BMI Z-score</td>
<td>2.23 ± 0.47</td>
</tr>
<tr>
<td>Tanner 4-5</td>
<td>84%</td>
</tr>
<tr>
<td>Female</td>
<td>65%</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>20%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>41%</td>
</tr>
<tr>
<td>Black</td>
<td>32%</td>
</tr>
<tr>
<td>American Indian</td>
<td>6%</td>
</tr>
<tr>
<td>GDM</td>
<td>33%</td>
</tr>
<tr>
<td>Acanthosis</td>
<td>86%</td>
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</tbody>
</table>
## More Baseline Characteristics

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<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Family Hx Diabetes</td>
<td>Nuclear</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>Nuclear + grands</td>
<td>89%</td>
</tr>
<tr>
<td>Lives with</td>
<td>Both parents</td>
<td>39%</td>
</tr>
<tr>
<td></td>
<td>Mother only</td>
<td>47%</td>
</tr>
<tr>
<td>Parental Education</td>
<td>High school or less</td>
<td>26%</td>
</tr>
<tr>
<td></td>
<td>College or more</td>
<td>17%</td>
</tr>
<tr>
<td>Household Income</td>
<td>&lt; $25,000</td>
<td>42%</td>
</tr>
<tr>
<td></td>
<td>&gt; $50,000</td>
<td>25%</td>
</tr>
</tbody>
</table>
The TODAY Cohort – comorbidities at baseline

The TODAY Cohort – comorbidities at baseline

- BP > 90th
- BP > 95th
- Albumin/creatinine
- LFTs
- LDL
- HDL
- Triglycerides

The Today Study Group
J Clin Endocrinol Metab 96:159-67, 2010
TODAY Cohort

- Predominantly minority and female
- Late pubertal (girls average 1 year younger than boys)
- BMI well above minimal eligibility requirement $\geq 85^{th}$ percentile
- T2D of very recent onset
- High prevalence of comorbidities
  - Families with
    - strong history of diabetes
    - limited educational attainment
    - low income
- < 50% living with two biological parents
What have we learned about the Cohort so far?

A Clinical Trial to Maintain Glycemic Control in Youth with Type 2 Diabetes

TODAY Study Group*

APRIL 29TH, 2012
319 of 699 = 45.6% experienced PO over a maximum 72 months of follow-up

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Failure rate</th>
<th>Median time to failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met + rosi</td>
<td>90 of 230 = 38.6%</td>
<td>10.3 months</td>
</tr>
<tr>
<td>Met + lifestyle</td>
<td>109 of 234 = 46.6%</td>
<td>12.0 months</td>
</tr>
<tr>
<td>Met alone</td>
<td>120 of 232 = 51.7%</td>
<td>11.8 months</td>
</tr>
</tbody>
</table>
Time-to-event Analysis

Failure Rates
- M: 51.7%
- M+R: 38.6%
- M+L: 46.6%

Pairwise Tests
- M+L vs. M+R: p=0.15
- M vs. M+R: p=0.006
- M vs. M+L: p=0.17

Proportion not experiencing glycemic failure vs. Time from randomization in months

Number at Risk
- 699 at 0 months
- 542 at 12 months
- 425 at 24 months
- 297 at 36 months
- 187 at 48 months
- 92 at 60 months
Change in % Overweight from Baseline

6 Months
- M vs. M+R p=.0009
- M vs. M+L p=.0058
- M+R vs. M+L p<.0001

24 Months
- M vs. M+R p=.0009
- M vs. M+L p=.5563
- M+R vs. M+L p<.0001
At Least 7 Percentage Point Reduction in % Overweight from Baseline

![Graph showing percent of participants over 6 and 24 months with reduction in overweight.]

- * p<.05 vs. M+R
- ** p<.001 vs. M+R
Failure by Gender and Race-Ethnicity

- **Gender**
  - Female 200 out of 452 = 44.3%
  - Male 119 out of 247 = 48.2%

- **Race-ethnicity**
  - NH Black 120 out of 227 = 52.9%
  - Hispanic 125 out of 279 = 44.8%
  - NH White 52 out of 141 = 36.9%
  - American Indian 16 of 41 = 39.0%
Primary Outcome Analysis – Females

Proportion not experiencing glycemic failure

Failure Rates
- M 52.1%
- M+R 31.6%
- M+L 49.4%

Pairwise Tests
- M+L vs. M+R p=0.006
- M vs. M+R p=0.002
- M vs. M+L p=0.65

Number at Risk
- Time from randomization in months

0 12 24 36 48 60
- 452 343 275 189 123 57
Primary Outcome Analysis – Males

Failure Rates
- M: 51.2%
- M+R: 51.9%
- M+L: 41.3%

Pairwise Tests
- M+L vs. M+R: p=0.14
- M vs. M+R: p=0.70
- M vs. M+L: p=0.061

Proportion not experiencing glycemic failure vs. Time from randomization in months

Number at Risk: 247, 199, 150, 108, 64, 35
Primary Outcome Analysis – NH Blacks

Failure Rates
- M: 66.2%
- M+R: 43.8%
- M+L: 47.7%

Pairwise Tests
- M+L vs. M+R: p=0.64
- M vs. M+R: p=0.003
- M vs. M+L: p=0.008

Proportion not experiencing glycemic failure

Number at Risk
- Time from randomization in months

0 12 24 36 48 60
227 164 129 86 53 26
Primary Outcome Analysis – Hispanics

Failure Rates
- M: 44.0%
- M+R: 41.6%
- M+L: 50.0%

Pairwise Tests
- M+L vs. M+R: p=0.17
- M vs. M+R: p=0.78
- M vs. M+L: p=0.29

Proportion not experiencing glyemic failure

Time from randomization in months

Number at Risk

278 224 168 119 75 36
Primary Outcome Analysis – NH Whites

Failure Rates
- M: 44.9%
- M+R: 25.5%
- M+L: 39.1%

Pairwise Tests
- M+L vs. M+R: p=0.25
- M vs. M+R: p=0.07
- M vs. M+L: p=0.50

Proportion not experiencing glycemic failure

Time from randomization in months

Number at Risk

0 12 24 36 48 60
142 114 97 67 46 23
Summary

- Half of participants on metformin monotherapy experienced loss of glycemic control, with a median time of 11 months.
- Addition of rosiglitazone reduced loss of glycemic control by 23%, though median time to failure was unchanged.
- Intensive lifestyle promoted more weight loss at 6 months than metformin alone, but this did not translate to improvement in sustained glycemic control.
- Gender and racial-ethnic differences in response to treatments are noted that require further analysis.
Implications

- Metformin monotherapy is inadequate for half of youth with type 2 diabetes.
- Early addition of a second agent may be required.
  - Given current concerns about rosiglitazone, the nature of this second agent requires further study.
- The role of intensive lifestyle interventions in youth with type 2 diabetes is uncertain.
- Nearly half of youth with type 2 diabetes maintain long-term control irrespective of treatment.
- Gender and racial-ethnic differences suggest the need for individualization of therapy.
Thank you for your attention