Update on type 2 diabetes in youth

Phil Zeitler MD, PhD
Section of Endocrinology
Department of Pediatrics
University of Colorado School of Medicine
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 and outcome

To compare three treatment regimens on time loss of glycemic control

- Metformin
- Metformin + rosiglitazone
- Metformin + intensive lifestyle

Outcome

- HbA1c ≥ 8.0% for at least 165 days (5½ months) or ended TODAY ≥ 10%.
- Inability to wean from temporary insulin therapy due to metabolic decompensation (forced wean by algorithm).

RCT Study Design

- 2-6 month pre-randomization run-in period
  - Provide standard diabetes education
  - Wean off all other diabetes medications
  - Titrate metformin as tolerated
    - Maximum 1000 mg bid
    - Minimum 500 mg bid
  - Assess ability to adhere to protocol
  - HbA1c < 8.0%
- Eligible and consented participants randomized to one of 3 treatment arms
- 4 year rolling enrollment period
- 2-6 years follow-up with medical visits every 2 months in year 1 and quarterly thereafter

Screening
N = 1211

Exclusions, N = 284
Positive antibodies 116 (9.6%)
C-peptide < 6 14 (1.1%)
Transaminase > 2.5 ULN 17 (1.4%)
Other 137 (11.3%)

Run-in
N = 927
(76.5%)

Randomization
N = 699
(57.7%)

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%)
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</td>
<td>= 38.6%</td>
</tr>
<tr>
<td>Met + lifestyle</td>
<td>109 of 234</td>
<td>= 46.6%</td>
</tr>
<tr>
<td>Met alone</td>
<td>120 of 232</td>
<td>= 51.7%</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

**Number at Risk**
- 699
- 542
- 425
- 297
- 187
- 92

**Time from randomization in months**

Change in % Overweight

6 Months

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>M</td>
<td>M+R</td>
</tr>
<tr>
<td></td>
<td>M+L</td>
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</tbody>
</table>

24 Months

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>M</td>
<td>M+R</td>
</tr>
<tr>
<td></td>
<td>M+L</td>
</tr>
</tbody>
</table>

M vs. M+R p = 0.0009
M vs. M+L p = 0.0058
M+R vs. M+L p < 0.0001

M vs. M+R p = 0.0009
M vs. M+L p = 0.5563
M+R vs. M+L p < 0.0001

### 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%

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

Males

Proportion not experiencing glycemic failure

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

Time from randomization in months

Number at Risk

247 199 150 108 64 35
Hispanics

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

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

Number at Risk:
- 278 at 0 months
- 224 at 12 months
- 168 at 24 months
- 119 at 36 months
- 75 at 48 months
- 36 at 60 months
NH Whites

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

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
In univariate analysis, race-ethnicity, household income, presence of depression, A1c, and IGI at baseline are all predictors of risk for failure.

In multivariate analysis, only A1c and IGI remain significant.
  - Baseline A1c (after treatment with metformin and completion of run-in) is reflecting other determinants of increased risk of failure.
  - IGI is a less strong predictor of risk for failure than A1c.
    - Beta cell function likely strongly reflected in A1c.
Baseline A1c is the primary predictor of likelihood of failure (irrespective of therapy).
  - Patients who do not normalize their A1c on metformin alone within a few months appear to be at higher risk of failure on therapy.
Over time in treatment, rising A1c – even though in the normal range – is associated with failure.
  - Rising A1c suggests the need to intensify treatment early, even while the patient has an A1c below 6.5%.
These relationships are not affected by treatment group, race-ethnicity, or sex.
Comorbidities and complications
Hypertension

A. Treatment Group, p=0.2705

M
M+R
M+L

Did not fail
Failed

B. Glycemic Failure, p=0.9541

C. Race-Ethnicity, p=0.7284

D. Gender, p<0.0001

Diabetes Care 36:1735-1741, 2013
Microalbumin

A. Treatment Group, p=0.4913  B. Glycemic Failure, p<0.0001  C. Race-Ethnicity, p=0.2032  D. Gender, p=0.2559

Diabetes Care 36:1735-1741, 2013
### Percent in High Risk Categories by Treatment and Visit

<table>
<thead>
<tr>
<th>Visit</th>
<th>LDL $\geq 130$ mg/dL or statin or sequestrant</th>
<th>HDL F$\leq 50$, M$&lt;40$ mg/dL</th>
<th>TG $\geq 150$ mg/dL or fibrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base</td>
<td>M</td>
<td>M+R</td>
<td>M+L</td>
</tr>
<tr>
<td></td>
<td>4.8%</td>
<td>4.8%</td>
<td>3.9%</td>
</tr>
<tr>
<td>M12</td>
<td>9.4%</td>
<td>7.6%</td>
<td>9.0%</td>
</tr>
<tr>
<td>M24</td>
<td>11.0%</td>
<td>8.8%</td>
<td>9.8%</td>
</tr>
<tr>
<td>M36</td>
<td>11.4%</td>
<td>12.1%</td>
<td>8.7%</td>
</tr>
</tbody>
</table>

Diabetes Care 36:1758-64, 2013
## Percent in High Risk Categories by Treatment and Visit

<table>
<thead>
<tr>
<th>Visit</th>
<th>hsCRP &gt;0.3 mg/dL</th>
<th>ApoB ≥110 mg/dL</th>
<th>Small dense LDL ≤0.263 Rf</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>M+R*</td>
<td>M+L</td>
</tr>
<tr>
<td>Base</td>
<td>44.1%</td>
<td>37.2%</td>
<td>42.2%</td>
</tr>
<tr>
<td>M12</td>
<td>41.5%</td>
<td>29.0%</td>
<td>31.9%</td>
</tr>
<tr>
<td>M24</td>
<td>41.7%</td>
<td>32.1%</td>
<td>35.1%</td>
</tr>
<tr>
<td>M36</td>
<td>53.2%</td>
<td>44.8%</td>
<td>41.8%</td>
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</table>

Diabetes Care 36:1758-64, 2013
Regression of Lipid on HbA1c Adjusted for BMI by Treatment Group

A. LDL versus HbA1c

- For LDL there was no difference across treatments but there was a significant positive slope (3.0%, p<0.0001).

B. Triglycerides versus HbA1c

- For triglycerides there was a significant difference across treatment groups (p=0.0250); both M and M+R had significant positive slopes (17 mg/dL, p=0.0240, and 23 mg/dL, p=0.0105, respectively) but M+L was flat.
Regression of Lipid on HbA1c Adjusted for BMI by Treatment Group

C. Treatment differences were not significant (p=0.0887) although M+R had a significantly negative slope (-2 mg/dL, p=0.0314); the slope for M was not significant (p=0.0972).

D. No treatment difference (p=0.0871) but M+R had a significantly negative slope (-1.6 mg/dL, p=0.0419).

Diabetes Care 36:1758-64, 2013
No subjects had more than mild non-proliferative retinopathy (NPDR)

No subjects had macular edema

Subjects were scored as:
  • retinopathy / no retinopathy
## Retinopathy

<table>
<thead>
<tr>
<th>Mean HbA1c %</th>
<th>N</th>
<th>N</th>
<th>%</th>
<th>Adjusted OR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.3-5.92</td>
<td>172</td>
<td>8</td>
<td>4.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.93-7.8</td>
<td>173</td>
<td>20</td>
<td>11.6</td>
<td>2.497</td>
<td>1.058-5.894</td>
</tr>
<tr>
<td>7.81-13.5</td>
<td>172</td>
<td>43</td>
<td>25.0</td>
<td>6.311</td>
<td>2.840-14.023</td>
</tr>
</tbody>
</table>

*Diabetes Care 36:1772-1774, 2013*
# Months since Diagnosis and Retinopathy

<table>
<thead>
<tr>
<th>Months</th>
<th>N</th>
<th>N</th>
<th>%</th>
<th>Adjusted OR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-49</td>
<td>170</td>
<td>9</td>
<td>5.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-66</td>
<td>172</td>
<td>23</td>
<td>13.4</td>
<td>1.974</td>
<td>0.842-4.628</td>
</tr>
<tr>
<td>67-101</td>
<td>175</td>
<td>39</td>
<td>22.3</td>
<td>3.649</td>
<td>1.504-8.848</td>
</tr>
</tbody>
</table>
Metformin monotherapy is inadequate for half of youth with type 2 diabetes.
The role of intensive lifestyle interventions in youth with type 2 diabetes is uncertain.
Youth with type 2 diabetes have high and increasing rates of hypertension, microalbuminuria, and dyslipidemia, as well as evidence for end organ cardiac damage.
Youth with type 2 diabetes have high rates of depression and come from families challenged by poverty, poor education and widespread poor health.
There are important race/ethnicity differences among youth with type 2 diabetes in the US.
Materials developed and used for the TODAY standard diabetes education program and the intensive lifestyle intervention program are available to the public at https://today.bsc.gwu.edu/.