Management of prediabetes to prevent progression to overt diabetes in Youth

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LEST WE THINK THIS IS NOT AN IMPORTANT PROBLEM

**Graph A**

- **T2DM**<sub>15-30</sub> = Hazard Ratio 2.0 (1.2-3.2)  \( P=0.003 \)

**Table**

<table>
<thead>
<tr>
<th>Duration of Diabetes (years)</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>&gt;30</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T2DM</strong>&lt;sub&gt;15-30&lt;/sub&gt;</td>
<td>354</td>
<td>334</td>
<td>297</td>
<td>247</td>
<td>188</td>
<td>134</td>
<td>83</td>
<td>56</td>
</tr>
<tr>
<td><strong>T1DM</strong>&lt;sub&gt;15-30&lt;/sub&gt;</td>
<td>470</td>
<td>454</td>
<td>422</td>
<td>366</td>
<td>293</td>
<td>210</td>
<td>142</td>
<td>95</td>
</tr>
</tbody>
</table>
Pathophysiology of Prediabetes
Definition of Diabetes

- **Diabetes**
  - **Symptomatic**
    - Fasting: > 126 mg/dl
    - Random: > 200
  - **Asymptomatic – all repeated on a different day**
    - Fasting > 126 mg/dl
    - Random > 200 mg/dl
    - Challenge (1.75 gm/Kg to max 75 gms):
      - 2 hour > 200

- **Prediabetes**
  - Impaired fasting glucose (IFG): 100 – 125 mg/dl
  - Impaired glucose tolerance (IGT): 140 – 200 mg/dl at 2 hours post challenge

ADA. Clinical practice recommendations—2015. Diabetes Care. 38(suppl 1)
ADA Hemoglobin A1c Criteria

- Assumes standardized laboratory A1c
- Prediabetes
  - A1c 5.7% to 6.4%
- Diabetes
  - A1c > 6.5%
    - Repeated if asymptomatic
- Caveats
  - Altered in some ethnic groups and with decreased RBC lifespan
  - Relevance to children and adolescents unknown

ADA. Clinical practice recommendations—2015. Diabetes Care. 2015;38(suppl 1)
The Prevalence of IFG is high

- NHANES 1999-2000
  - Obese Adolescents 11.7%
- STOPP-T2D - 2006
  - 40.5% IFG
Metabolic syndrome in overweight Hispanic youth

Cruz et al. J Clin Endocrinol Metab 89:108-113, 2004
A1c and screening for prediabetes

<table>
<thead>
<tr>
<th>Pre-diabetes category</th>
<th>N</th>
<th>F/U %</th>
<th>Mean time of F/U (months)</th>
<th>N (%) with T2D</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPG &gt; 140 mg/dl</td>
<td>11</td>
<td>63.6%</td>
<td>15.0</td>
<td>0</td>
</tr>
<tr>
<td>FPG &gt; 100 mg/dl</td>
<td>42</td>
<td>64.3%</td>
<td>26.4</td>
<td>5 (18.5%)</td>
</tr>
<tr>
<td>A1c 5.7-5.9% (mild)</td>
<td>206</td>
<td>39.3%</td>
<td>8.9</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>A1c 6.0-6.4% (moderate)</td>
<td>58</td>
<td>69.0%</td>
<td>11.6</td>
<td>7 (18.4%)</td>
</tr>
</tbody>
</table>

Glucose Homeostasis

- Balance Between Insulin action and secretion
- Diabetes occurs when this balance is lost
Relationship Between Insulin Sensitivity and Insulin Response in Apparently Healthy Subjects

The Relationship Between Insulin Secretion and Insulin Action During the Development of Type 2 Diabetes
Insulin Secretion and Insulin Action in the Development of Type 2 Diabetes

B-cell function is impaired in obese adolescents with “normal” 2-hour glucose
B-cell dysfunction is impaired in obese adolescents with normal fasting glucose and is BMI dependent.

Tfayli et al Diabetes Care 33:2024, 2010
102 obese children and adolescents

NGT
N=71

IGT
N=31

NGT
N=65 (91.5%)

IGT
N=6 (8.5%)

NGT
N=10 (32.3%)

IGT
N=11 (35.4%)

T2DM
N=10 (32.3%)

Mean follow-up of 21 months

Weiss R. et al Diabetes Care 28:902, 2005
Anthropometric Changes during the Evolution of IGT

Baseline OGTT 2 OGTT 3

Body Mass Index

NP
P

BMI-z score

NP
P

p=0.07

Total Body Fat

NP
P

Cali A et al., ADA 2008
Changes in Insulin Sensitivity, β-Cell Responsivity and Disposition Index during the Evolution Of IGT

Insulin Sensitivity

β-Cell Responsivity

Disposition Index

Cali A et al, ADA 2008
Insulin resistance and puberty

Moran et al J Clin Endocrinol Metab 87:4817, 2002
Regular and Ectopic Fat Depots

- Where can one store fat?
  - Subcutaneous fat
  - Visceral (intra-abdominal) fat
  - Insulin sensitive tissues
    - Liver
    - Muscle
    - Pancreas
  - Pericardial
  - Perivascular
Energy-dense food (↑ fat + sugar content) → Lack of physical activity/exercise → Positive energy balance → Subcutaneous obesity 'Healthy' adipose tissue → NO ECTOPIC FAT
- Low muscle fat
- Low epicardial fat
- Low liver fat and normal function

Visceral obesity Dysfunctional adipose tissue → LIPID OVERFLOW-ECTOPIC FAT
- ▲ Muscle fat (↑ intracellular lipid)
- ▲ Epicardial fat
- ▲ Liver fat and altered function

- Smoking
- 'Unfavourable' genotype
- Maladaptive response to stress
A “Central” Role for Central Obesity in Insulin Resistance

Intra-abdominal Fat

Glucose Disposal (mg/kg LBM·min)

Intra-Abdominal/Total Adipose Tissue
Increasing Insulin Resistance with High Visceral and Low Subcutaneous Abdominal Fat

*Adjusted for age, gender, race/ethnicity

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Taksali S. et al Diabetes 2008
Fatty Liver and Metabolic Pattern

Burgert T et al JCEM 2006
Treating Prediabetes
In principle, it’s easy!

► Reduce the accretion of visceral fat through lifestyle modification
► Reverse the trends in the toxic environment
  ▶ Reduce caloric intake
  ▶ Increase caloric expenditure
AAP Expert Committee:

- Evidence based dietary interventions
  - Eliminate liquid calories
  - Reduce or eliminate eating out
  - Reduce portion sizes

- Evidence based activity interventions
  - Reduce sedentary time/screen time
  - Encourage attainment of recommended activity goals.

Barlow et al Pediatrics 120:S164-192, 2007
Effects of lifestyle intervention in obese adults

Torgersen et al. *Diab Care* 27: 155, 2004
Pi-Sunyer et al. *JAMA* 295: 761, 2006
Effects of lifestyle intervention in obese children and adults

- Godoy-Matos et al. *JCEM* 90: 1460, 2005
- Nemet et al. *Pediatrics* 115: e443, 2005
- Chanoine et al. *JAMA* 293: 2873-2883, 2005
Cochrane Meta-analyses

- Summerbell 2007 – No evidence for effectiveness of school-based interventions for the prevention of obesity
  - Some evidence for reported changes in dietary habits

- Summberbell 2007 – No evidence for effectiveness of school-based interventions for the treatment of obesity
Pharmacologic intervention
Pharmacologic approaches to diabetes prevention (3 year data)

Torgerson et al. Diabetes Care 27: 155-161, 2004

Cumulative incidence of diabetes (%)

Mixed Race
-31%

Asian Indians
-26%

Swedes
-32%

STD
ORL

0 10 20 30 40 50 60
Diabetes Prevention Program (DPP)

- Clinical trial comparing diet and exercise or metformin to placebo in adults with impaired glucose tolerance
- DSMB stopped the trial a year early because the data had clearly answered the main research questions

Participant selection

- 3,234 participants
- 45% from minority groups
- Overweight (BMI ≥ 25 kg/m²)
- 40-65 years old
- Impaired glucose tolerance
  - Glucose 140-200 mg/dL 2 hrs after 75g glucose
  - Fasting glucose < 140 mg/dL
- Exclusion criteria
  - Diagnosis of diabetes mellitus
  - chronic disease with < 6 yr survival
Lifestyle Intervention

- 523 participants randomly assigned to:
  - Control received annual oral and written diet and exercise information
  - Intervention received tailored dietary and exercise advice by nutritionists
    - 7 times in 1\textsuperscript{st} year
    - Every 3 months thereafter

NEJM 344: 1343, 2001
Endpoints

- Diagnosis of diabetes
  - Fasting glucose > 140 mg/dl
  - Glucose > 200 mg/dl 2 hrs after 75g glucose challenge

NEJM 344: 1343, 2001
DPP: estimated cumulative incidence of type 2 diabetes in 3 years

![Bar chart showing estimated cumulative incidence of type 2 diabetes in 3 years for placebo, metformin, and lifestyle groups.](image)

- Placebo: 30 percent
- Metformin: 20 percent
- Lifestyle: 10 percent

*Statistically significant difference compared to placebo.
**Statistically significant difference compared to placebo.

DPP: effects of treatment on body weight

DPP: incidence of type 2 diabetes in subjects aged 25-44 years

DPP: incidence of type 2 diabetes in subjects with BMI > 34.9

Metformin in Youth

- Non-controlled case studies
- Freemark and Bursey
  - 29 obese adolescents
    - white and black
    - boys and girls
  - BMI > 30 kg/m², Fasting insulin > 15
  - At least 1 1° or 2° degree relative with T2DM
  - Metformin 500 mg BID or placebo for 6 months
  - BMI decreased 0.12 SD (1%) vs. increase of 0.23 SD (2%)
  - Decreased fasting glucose (all normal) and insulin
# Metformin in Youth

- Double blind placebo controlled 6 month-crossover trial
- Metformin 1000 mg twice a day or placebo
- 28 obese adolescents randomized
- 22 analyzed (78%)

<table>
<thead>
<tr>
<th></th>
<th>Size of treatment effect</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>– 4.35</td>
<td>0.02</td>
</tr>
<tr>
<td>Weight z-score</td>
<td>– 0.09</td>
<td>0.009</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>– 1.26</td>
<td>0.002</td>
</tr>
<tr>
<td>BMI z-score</td>
<td>– 0.12</td>
<td>0.005</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>– 2.8</td>
<td>0.003</td>
</tr>
<tr>
<td>Waist circumference z-score</td>
<td>– 0.05</td>
<td>0.005</td>
</tr>
<tr>
<td>Fasting glucose (mmol/liter)</td>
<td>– 0.2</td>
<td>0.048</td>
</tr>
</tbody>
</table>

Srinivasan et al. JCEM 2006
Metformin in Youth

Srinivasan et al JCEM 2006
Metformin in Youth

- 85 obese insulin-resistant adolescents
  - BMI > 95th percentile
  - Fasting insulin > 15 or HOMA > 2.5
- Randomized to receive metformin (1000 mg a day) or placebo for 6 months
- All participants received office-based lifestyle intervention
- 80% of metformin and 64% of placebo subjects completed 6 months

### Metformin in Youth– Decrease in BMI

<table>
<thead>
<tr>
<th></th>
<th>Metformin (N= 48)</th>
<th>Placebo (N= 16)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in BMI (Kg/m²)</td>
<td>-0.16 ± 1.89</td>
<td>0.63 ± 1.29</td>
<td>0.11</td>
</tr>
<tr>
<td>BMI decrease of &gt; 5%</td>
<td>11(22.9%)</td>
<td>0 (0.0%)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Increase in BMI</td>
<td>20 (41.7%)</td>
<td>11 (68.8%)</td>
<td>0.06</td>
</tr>
</tbody>
</table>
**Metformin in Youth– Adherence**

- **BMI change**
  - Metformin adherent: -0.32 kg/m²
  - Metformin non-adherent: 0.1 kg/m²
  - Placebo adherent: 0.63 kg/m²
  - Placebo non-adherent: 0.98 kg/m²

- **BMI decrease of 5%**
  - Metformin adherent: 26.7%
  - Metformin non-adherent: 16.7%
  - Placebo adherent: 0%
  - Placebo non-adherent: 0%

- **N**
  - Metformin adherent: 27
  - Metformin non-adherent: 18
  - Placebo adherent: 10
  - Placebo non-adherent: 5
**Metformin in Youth - lifestyle**

<table>
<thead>
<tr>
<th></th>
<th>Metformin Adherent Decrease portions N= 10</th>
<th>Metformin Adherent no decrease portions N = 17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in BMI (kg/m²)</td>
<td>-1.3 ± 1.5</td>
<td>0.4 ± 2.1</td>
</tr>
<tr>
<td>BMI decrease of &gt; 5%</td>
<td>6 (60.0%)</td>
<td>1 (5.9%)</td>
</tr>
</tbody>
</table>
DPP for Youth?

- Progression to diabetes is ~10% in 2 years among obese NHB youth in 2 years.
- Progression to diabetes is ~7% in 8 years in insulin-resistant Hispanic adolescents with NGT.
- Assume metformin reduces progression by the same order of magnitude as in IGT adults (~0.3% progression vs ~0.5% every 6 months).
- Assume 5% dropout every 6 months.
- Study would need 5000 kids and last 6 years to get 80% power to see the difference.
Bariatric Surgery: Weight Change

Adapted from Inge et.al. N Engl J Med. 2016 374:113-232015
Bariatric Surgery: comorbidities

<table>
<thead>
<tr>
<th>Condition</th>
<th>% at baseline</th>
<th>% remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 diabetes</td>
<td>13</td>
<td>90%</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>10</td>
<td>77%</td>
</tr>
<tr>
<td>dyslipidemia</td>
<td>76</td>
<td>66</td>
</tr>
<tr>
<td>HTN</td>
<td>43</td>
<td>73</td>
</tr>
</tbody>
</table>

Adapted from Inge et.al. N Engl J Med. 2016 374:113-232015
## Restoring Insulin Secretion (RISE) Study: Interventions

<table>
<thead>
<tr>
<th>Adult Medication</th>
<th>Pediatric Medication</th>
<th>Adult Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Metformin</td>
<td>1. Metformin</td>
<td>1. Metformin</td>
</tr>
<tr>
<td>2. Glargine followed by metformin</td>
<td>2. Glargine followed by metformin</td>
<td>2. Laparoscopic banding</td>
</tr>
<tr>
<td>3. Liraglutide plus metformin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Placebo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RISE Consortium Diabetes Care. 2014;37(3):780-
Restoring Insulin Secretion (RISE) Study: Design for Medication Arms

- Insulin Sensitivity
- iv β-cell Function

OGTT

Intervention

0 3 6 9 12 15

Months

RISE Consortium Diabetes Care. 2014;37(3):780-
Targeting Prediabetes

**Rationale**
- Source of many complications
- Weight loss reverses dysglycemia

**Limitations**
- Some individuals with prediabetes will revert spontaneously to normal glucose tolerance.
- Dramatic weight loss unusual with lifestyle interventions or medications
- Weight loss goals unclear – amount of weight loss needed is unknown
- Duration of treatment – is pharmacologic intervention lifelong?
- Pharmacologic intervention – preventing diabetes or treating diabetes?
Treating Diabetes

Rationale
- Endpoints clearly defined and related to clinical disease
- Guidelines for treatment available
- Diagnosed disease may be more motivating
- Insurance coverage

Limitations
- Diabetes might progress to “state of irreversibility” even in absence of obvious complications
- Waiting for some complications to emerge (e.g. atherogenesis) may be waiting until it’s too late
Thank you for your attention