Prevention of Exercise Induced Hypoglycemia in Youth with Type 1 Diabetes Mellitus (T1DM)

Justin Gregory, M.D., M.S.C.I.
Assistant Professor of Pediatrics
Vanderbilt University School of Medicine
Disclosure

I have no actual or potential conflict of interest in relation to this presentation
Kris Freeman, Vancouver, 2010

"I don't identify myself as a diabetic, I identify myself as a cross-country skier."

Skier slowed, not stopped, by diabetes.
Overview and Goals

1. Establish advantages of exercise in T1DM
   – “The Big Benefit”

2. Contrast metabolic regulation during exercise between individuals with and without T1DM
   – “The Major Malfunction”

3. Outline principals of glycemic management before, during, and after exercise in pediatric individuals with T1DM
   – “The Preventative Principals”
Part 1: So Why Exercise?
Exercise is a Standard of Care

Children and adolescents with type 1 or type 2 diabetes or prediabetes should engage in 60 min/day or more of moderate- or vigorous-intensity aerobic activity, with vigorous muscle-strengthening and bone-strengthening activities at least 3 days/week.

# Benefits vs. Risks of Exercise

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Potentially lowers HbA1c</td>
<td></td>
</tr>
</tbody>
</table>

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0058861
Benefits vs. Risks of Exercise

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Potentially lowers HbA1c</td>
<td></td>
</tr>
<tr>
<td>• Reduces risk of CVD, HTN, colon cancer, obesity, osteoporosis</td>
<td></td>
</tr>
<tr>
<td>• Increases overall life expectancy</td>
<td></td>
</tr>
</tbody>
</table>

Mortality and life expectancy in T1DM

Even minimal exercise reduces mortality in large population studies

## Benefits vs. Risks of Exercise

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Potentially lowers HbA1c</td>
<td></td>
</tr>
<tr>
<td>• Reduced risk of CVD, HTN, colon cancer, obesity, osteoporosis</td>
<td></td>
</tr>
<tr>
<td>• Increased overall life expectancy</td>
<td></td>
</tr>
<tr>
<td>• Increases CV endurance and fitness</td>
<td></td>
</tr>
<tr>
<td>• Increases whole body insulin sensitivity</td>
<td></td>
</tr>
</tbody>
</table>

Exercise normalizes insulin sensitivity in T1DM

Benefits vs. Risks of Exercise

Benefits

- Potentially lowers HbA1c
- Reduced risk of CVD, HTN, colon cancer, obesity, osteoporosis
- Increased overall life expectancy
- Increases CV endurance and fitness
- Increases whole body insulin sensitivity
- Enhanced self-esteem and sense of well being

Risks

- Musculoskeletal injury
- CV accident (angina, MI, sudden death)
- Worsening of underlying retinopathy and neuropathy

Benefits vs. Risks of Exercise

**Benefits**
- Potentially lowers HbA1c
- Reduced risk of CVD, HTN, colon cancer, obesity, osteoporosis
- Increased overall life expectancy
- Increases CV endurance and fitness
- Increases whole body insulin sensitivity
- Enhanced self-esteem and sense of well being

**Risks**
- Musculoskeletal injury
- CV accident (angina, MI, sudden death)
- Worsening of underlying retinopathy and neuropathy
  - Hyperglycemia
  - Hypoglycemia

Part 1 Conclusion

• To attain the significant benefits of exercise in T1DM, adequate attention must be given to its associated risks.
Part 2: How is metabolic regulation during exercise different between individuals with and without T1DM?
AEROBIC EXERCISE IN THE NON-T1DM STATE

In a remarkably coordinated fashion, the body makes hormonal adaptations to maintain a steady, normal plasma glucose concentration.
Galbo et al. 1976

- Six healthy young adult men exercised on a treadmill at 60% VO2 max
- Exercise continued until exhaustion (160 min on average)
90 mg/dL
72 mg/dL
Plasma epinephrine (ng/mL)  Plasma norepinephrine (ng/mL)

Despite rapid increases in glucose utilization, glucose remains normal throughout > 2½ hours of exercise. Why?

- Maintains glucose for brain
- Source of energy for working muscle as muscle glycogen becomes depleted

Despite rapid (insulin-independent) increases in glucose utilization, glucose remains normal throughout > 2½ hours of exercise. How?

- At first, muscle uses its stored glucose (muscle glycogen)
- Pretty soon, glucose utilization by muscle is closely matched by glucose production by liver

How does liver increase glucose production?

- **Glycogenolysis (first)**
  - Decreasing insulin
  - Increasing glucagon
- **Gluconeogenesis (later)**
  - Epinephrine stimulates
    - Lipolysis -> glycerol
    - Lactate production

Aerobic Exercise in T1DM is frequently accompanied by metabolic dysfunction

1. Frequently, insulin delivery is mismatched to exercise leading to overinsulinization
2. Counterregulatory mechanisms that raise glucose production to match the muscle’s needs are often defective
Reasons for overinsulinization

1. When exercise begins, insulin in the blood does not fall like it does in nondiabetic individuals

2. Insulin action increases during and after exercise, leading to relative overinsulinization

Insulin sensitivity improves after 12 weeks of moderate exercise (80% VO2 max) in T1DM

<table>
<thead>
<tr>
<th>Response before and after 12 wk</th>
<th>Exercise group (N = 9)</th>
<th>Control group (N = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Glucose utilization rate (mg/M²/min)</td>
<td>274 ± 33</td>
<td>338 ± 28</td>
</tr>
</tbody>
</table>

Insulin sensitivity is acutely affected by exercise

Reasons for overinsulinization

1. When exercise begins, insulin in the blood does not fall like it does in nondiabetic individuals
2. Insulin action increases during and after exercise, leading to relative overinsulinization
3. Exercise can accelerate the absorption of subcutaneously-injected insulin

Effect of leg exercise and injection site on insulin absorption

Effect of leg exercise and injection site on change in plasma glucose

Reasons for counterregulatory hormone deficiency

- Autonomic failure
- Antecedent hypoglycemia
Antecedent hypoglycemia results in severely diminished counterregulatory response to exercise in T1DM

The lack of a counterregulatory response leads to diminished endogenous glucose production to power exercise.

Part 2 Conclusion

• Exercise associated hypoglycemia in Type 1 diabetes is directly attributable to the difficulty of mimicking the physiologic response to exercise
Part 3: Management of glycemia before, during, and after exercise in pediatric individuals with T1DM, a case-based approach
Case 1: Aerobic exercise

• 16 YOF with 4 year H/O T1DM, eats school lunch at 11 AM, has cross-country practice (running at ~80% VO2 max for 60-90 min) at 3 PM.
• She is using a multiple daily injection (MDI) insulin regimen, with glargine 20 u q HS and aspart at mealtimes, 1 unit : 10 gm carb.

Case 1: Aerobic exercise

• Despite taking aspart 4 hours before exercise she is forlorn because she cannot control hypoglycemia during exercise.

• Task: Determine whether hypoglycemia is occurring because there is
  – Too much insulin on-board from lunch injection (aspart)
  – Excessive basal insulin (glargine) for exercise
  – Too few extra carbs
Pharmacokinetic profile for rapid vs basal insulin analogs


Approach 1: pound sugar before and during exercise

“Oh no.. my blood sugar is low....”

“I DON’T ALWAYS EAT CAKE
BUT WHEN I DO, DIABEETUS

“Wait.. that means I can eat anything I want!!!!”
“Drink gatorade approach”

- 20 adolescents w/ T1DM
- Ate breakfast and injected insulin per routine
- 100 min after breakfast began cycle ergometer at ~60% VO2 max (145-160 bpm) for 60 min.
- CHO consumption was measured using indirect calorimetry during a control experiment where H2O was consumed
- In a second experiment, an equivalent amount of carbohydrate was consumed in a sports drink (87.3 ± 5.1 g = 207 ± 8 mL = 7 US fl. oz.)

### Stratified approach to carb intake

<table>
<thead>
<tr>
<th>Pre-Exercise BG Concentration</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;90 mg/dL</td>
<td>Ingest 15–30 g of fast-acting carbohydrates before the onset of exercise, depending on the size of the individual. Follow with extra carbs throughout exercise.</td>
</tr>
<tr>
<td>90–149 mg/dL</td>
<td>Start consuming extra carbs at the onset of exercise (~0.5–1.0 g/kg body mass/hour of exercise), depending on the energy expenditure and the amount of circulating insulin at the time of exercise.</td>
</tr>
<tr>
<td>150–249 mg/dL</td>
<td>Initiate exercise and delay consumption of extra carbs until blood glucose levels drop to &lt;150 mg/dL.</td>
</tr>
<tr>
<td>250–349 mg/dL</td>
<td>Test for ketones: do not perform any exercise if moderate to large amounts of ketones are present. Initiate mild- to moderate-intensity exercise. Intense exercise should be delayed until glucose levels drop to &lt;250 mg/dL because intense exercise may exaggerate the hyperglycemia.</td>
</tr>
<tr>
<td>≥350 mg/dL</td>
<td>Test for ketones: do not perform any exercise if moderate to large amounts of ketones are present. If ketones are negative (or trace), consider conservative insulin correction (e.g., 50% correction) before exercise, depending on current “on board” (active) insulin status. Initiate mild to moderate exercise and avoid intense exercise (aerobic or anaerobic) until glucose levels drop.</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Race/ethnicity</th>
<th>Nondiabetic youth estimate*</th>
<th>SEARCH participants by diabetes type</th>
<th></th>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (95% CI)**</td>
<td>Total</td>
<td>N</td>
<td>% (95% CI)**</td>
<td>Total</td>
<td>N</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHW</td>
<td>15.8 (14.3, 17.5)</td>
<td>2647</td>
<td>287</td>
<td>10.7 (9.5,11.9)#*</td>
<td>82</td>
<td>64</td>
</tr>
<tr>
<td>AA</td>
<td>20.2 (18.6, 21.9)</td>
<td>310</td>
<td>69</td>
<td>20.1 (15.9,25.4)#*</td>
<td>133</td>
<td>111</td>
</tr>
<tr>
<td>Hispanic</td>
<td>18.3 (16.2,20.5)</td>
<td>414</td>
<td>71</td>
<td>17.0 (13.7,21.0)#*</td>
<td>91</td>
<td>63</td>
</tr>
<tr>
<td>API</td>
<td>132</td>
<td>22</td>
<td>16.6 (10.8,24.6)#*</td>
<td>45</td>
<td>34</td>
<td>68.2 (43.4,85.7)#*</td>
</tr>
<tr>
<td>AI</td>
<td>21</td>
<td>1</td>
<td>0.0 (0.0,100.0)#*</td>
<td>78</td>
<td>59</td>
<td>88.0 (67.9,96.2)#*</td>
</tr>
<tr>
<td>All</td>
<td>16.9 (15.8,18.0)</td>
<td>3524</td>
<td>450</td>
<td><strong>12.6 (11.5,13.8)</strong>#*</td>
<td>429</td>
<td>331</td>
</tr>
<tr>
<td>Overweight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHW</td>
<td>15.9 (14.3,17.6)</td>
<td>2647</td>
<td>546</td>
<td>20.8 (19.3,22.5)#*</td>
<td>82</td>
<td>10</td>
</tr>
<tr>
<td>AA</td>
<td>14.8 (13.4,16.3)</td>
<td>310</td>
<td>75</td>
<td>23.4 (18.7,28.9)#*</td>
<td>133</td>
<td>15</td>
</tr>
<tr>
<td>Hispanic</td>
<td>18.8 (16.6,21.1)</td>
<td>414</td>
<td>115</td>
<td>28.0 (23.9,32.6)#*</td>
<td>91</td>
<td>11</td>
</tr>
<tr>
<td>API</td>
<td>132</td>
<td>36</td>
<td>24.4 (17.2,33.5)</td>
<td>45</td>
<td>7</td>
<td>14.9 (4.4,39.9)</td>
</tr>
<tr>
<td>AI</td>
<td>21</td>
<td>3</td>
<td>15.0 (4.3,40.9)</td>
<td>78</td>
<td>7</td>
<td>3.3 (0.4,20.7)</td>
</tr>
<tr>
<td>All</td>
<td>16.1 (15.0,17.3)</td>
<td>3524</td>
<td>775</td>
<td><strong>22.1 (20.8,23.6)</strong>#*</td>
<td>429</td>
<td>50</td>
</tr>
</tbody>
</table>
Approach 2: Drop basal insulin (glargine)

• Approach 2a
  – decrease dose by 10-20% the night before
  – risk: nocturnal hyperglycemia

• Approach 2b
  – Try an insulin analog with a somewhat shorter duration (detemir), break up the dosage into BID dosing and make a 10-20% reduction in the morning dose
  – Risk: more complex, increased likelihood of dosage omission
Approach 3: Frequent BG monitoring and Insulin Pump Therapy

- Increases flexibility with basal insulin
  - Basal rate reductions should be made 60–90 minutes before the onset of exercise and should last until the activity is completed.
  - Individuals should test their glucose levels frequently and resume basal insulin delivery or provide bolus delivery if glucose levels are rising toward the hyperglycemic range.

<table>
<thead>
<tr>
<th>Aerobic Exercise Intensity</th>
<th>Basal Rate Reduction for 60 Minutes of Exercise (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>30</td>
</tr>
<tr>
<td>Moderate</td>
<td>50</td>
</tr>
<tr>
<td>Intense</td>
<td>90–100</td>
</tr>
</tbody>
</table>

Approach 3: Frequent BG monitoring and Insulin Pump Therapy

- Because the basal rate reduction lasts as long as the exercise, post-exercise hyperglycemia occurs less often

Approach 3: Frequent BG monitoring and Insulin Pump Therapy

- Increases flexibility with basal insulin
- Continuous glucose monitoring (CGM) allows for titration in carbohydrate intake as needed

<table>
<thead>
<tr>
<th>Sensor Glucose (mg/dL)</th>
<th>Trend Arrows</th>
<th>Carbohydrate Intake (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>109–124</td>
<td>↓ or ↓↓</td>
<td>8 (2 glucose tablets)</td>
</tr>
<tr>
<td>90–108</td>
<td>↓</td>
<td>16 (4 glucose tablets)</td>
</tr>
<tr>
<td></td>
<td>↓↓</td>
<td>20 (5 glucose tablets)</td>
</tr>
<tr>
<td>&lt;90</td>
<td>No arrow</td>
<td>16 (4 glucose tablets)</td>
</tr>
<tr>
<td></td>
<td>↓ or ↓↓</td>
<td>20 (5 glucose tablets)</td>
</tr>
</tbody>
</table>

Carb intake algorithm coupled with CGM can prevent hypoglycemia

Case 2: Endurance and strength training

- 17 YOM with 10 year H/O T1DM who is otherwise well wants to do Crossfit
- Takes insulin lispro with an insulin pump and monitors glucose with CGM

Case 2: Endurance and strength training

- He is also despondent:
  - His exercise regimen consists of a 30-45 min aerobic session, followed by 20-30 minutes of weight training
  - Although his HbA1c is at target (7.0%), uses a CGM, exercises > 4 hours after his last meal bolus and reduces the basal rate by 30% at the onset of exercise, and starts exercise with glucose in the mid 100s, he usually experiences hypoglycemia during his workout
  - His glucose sensor appears to be “off” or delayed compared with his BG monitor during exercise
Task: Determine the problems:

1. Apparent CGM inaccuracy:
   - Exercise does not affect sensor accuracy *per se*.
   - Delay in equilibrium occurs between capillary blood glucose (what brain senses) and adipose interstitial fluid glucose (what CGM measures)
   - “Lag time” has been reported to be 5-28 minutes, depending on experimental conditions and sensor calibration
   - If blood glucose is changing rapidly, there will often be a pronounced mismatch between sensor values and actual blood glucose values

Task: Determine the problems:

2. Timing of basal rate reduction:
   - Should ideally start 60-120 minutes before onset of exercise
Task: Determine the problems:

3. Order of exercise:
   - Generally, aerobic exercise decreases glucose while resistance exercise increases glucose in T1DM.
   - Reversing the order of aerobic and anaerobic exercise might help prevent hypoglycemia.

Resistance then aerobic exercise leads to a more favorable glycemic profile

**Start**
Is the activity being done in a fasting or post-absorptive state with low levels of bolus insulin on board?

- **Yes**
  - Consider basal insulin dose reduction or a carbohydrate snack (or both)†

- **No**
  - Can the bolus insulin given at mealtime be reduced?
    - **Yes**
      - Reduce bolus insulin by 25–75% at the meal before exercise depending on the intensity of activity (25% for light exercise, 50% for moderate exercise, and 75% for high intensity exercise)∗††
    - **No**
      - Consider increased carbohydrate intake at a rate of ~0.5–1.0 g per kg body mass per h of activity, depending on the intensity and duration of activity and blood glucose concentrations∗†

- **Is the patient on CSII?**
  - **Yes**
    - Reduce basal insulin by 50–80% up to 90 min before the start of exercise until the exercise stops.∗ Or consider pump suspension at the start of exercise (suspend insulin for no longer than 60 min).∗ Consume additional carbohydrates as needed on the basis of glucose monitoring (eg, 10–20 g/h)*
  - **No**
    - Consume additional carbohydrates as needed (eg, 20–30 g/h).∗ Consider a 20% reduction in basal insulin on days with prolonged activity*

- For first meal consumed after exercise (within 90 min), consider consumption of 1.0–1.2 g/kg of carbohydrate and reduction of insulin bolus by ~50%; to reduce risk of delayed nocturnal hypoglycaemia, especially if exercise occurs in the afternoon or evening, reduce overnight basal insulin by 20%, or consume a bedtime snack without insulin
Part 3 Conclusions

• A systematic approach to exercise that seeks to mimic physiology utilizing existing technologies (insulin pump, CGM) leads to incremental improvements in the frequency, duration, and magnitude of hypoglycemia.
“True, it is a fight, but there is pleasure in the struggle. Victory comes to the courageous; and without courage and common sense, success awaits no one. I look upon the diabetic as charioteer and his chariot as drawn by three steeds named Diet, Insulin, and Exercise. It takes skill to drive one horse, intelligence to manage a team of two, but a man must be a very good teamster who can get all three to pull together.” E.P. Joslin, 1933
Principal references

1. Meneghini, Luigi. Exercise and Type 1 Diabetes. Presentation at Vanderbilt University Endocrinology Grand Rounds


Questions?