OBESITY AND TYPE 2 DIABETES

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Disclosures

I will discuss off label medication use as many adult T2D drugs are NOT approved for use in pediatric patients
PEDIATRIC OBESITY
TENNESSEE
Overweight: 17.1%
Obese: 18.6%
June, 2013

American Medical Association recognizes obesity as a disease
Why does childhood obesity matter?

The risk of adult obesity is at least DOUBLED in obese children.
Led by Vanderbilt and the Tennessee Department of Health

*Eat Well Play More Tennessee*

RESULTS

• Decline in overweight, obesity and extreme obesity
• Sharper declines among African Americans and major metropolitan areas
• National rankings improved: 3rd → 8th (2009-2010)
Pediatricians and Obesity

• Pediatricians report feeling helpless about obesity

• According to the AAP survey
  – 92% feel comfortable counseling patients
  – But only 38% think counseling helps
  – 69% reported that weight loss programs weren’t covered by insurance
Exercise and Insulin Resistance-Induced CVD

- Improved Insulin Sensitivity
- Reduced Hyperinsulinemia
- eNOS activity
- ET-1
- NO
- Endothelial Dysfunction
- Oxidative Stress
- Inflammatory Markers
- Endothelial Regenerative Capacity
- Endothelial Progenitor Cells

Cardiovascular Protection

- Blood Flow and Capillary Perfusion
- Glucose Uptake and Metabolism
- Endurance and Functional Capacity

Phillips et al. Progress in CV Disease 2014
Weight Management Programs

• Yale Bright Bodies- a weight management program for inner city youth
  – Structured meal plan vs nutrition education/exercise program
    • 83% of structured meal patients dropped out in the first 6 months
  – Continued to compare the education/exercise group with a control group (2:1)
  – Patients 8-16yo and their parents

Savoye et al. JAMA 2007
Yale Bright Bodies

• Intervention group
  – Twice a week for 6 months, every other week for 6 months
  – Group exercise
  – 40 min of nutrition education per week

• Control group
  – Attended obesity clinic every 6 months
  – Counseled on weight loss strategies

Savoye et al. JAMA 2007
Yale Bright Bodies

- Intervention group: $\text{BMI} \downarrow 1.7 \text{ kg/m}^2$
  - stable weight with increasing height
- Control group: $\text{BMI} \uparrow 1.6 \text{ kg/m}^2$

- Differences between groups after 12mo
  - BMI -3.3 kg/m²
  - Weight -7.4 kg
  - Body fat -6%
- Sustained over 12 month follow up

Savoye et al. *JAMA* 2007
Savoye et al. *Pediatrics* 2011
Healthy Weight and Your Child
• 7-13yo WITH parent
• 4 month program
  • 2x per week x 10 weeks
  • 1x per week x 5 weeks

Locations
• Camp Widjiwagan
• Northwest (North Nashville)
• Robertson County

Empowering Families
to Live Healthier Lives
Exercise

- Goal: 60 minutes of moderate to vigorous activity per day
  - 10,000 steps per day
  - Walking pace: 20-30 minutes per mile
- Decline in activity during adolescence, especially in girls
  - PA tracks from adolescence to adulthood
- Improves bone health, mental health and cognitive skills

At baseline, 28.7 percent of adolescents met current physical activity guidelines for aerobic physical activity in 2011. The target is 31.6 percent, based on a target-setting method of 10 percent improvement.

Data Source: Youth Risk Behavior Surveillance System (YRBSS), CDC/NCHHSTP
Walking

5-12 year olds
• School based walking interventions have been most successful

13-18 year olds
• Pedometers may increase step counts

School Based Interventions

Recommended by the Community Preventive Services Task Force

- Goal: increase time spent in moderate-vigorous activity during Physical Education (PE)

- Strategies:
  - incorporate circuit training
  - modify rules of games to increase activity

Organized Sports

- Vigorous but NOT moderate sports correlate with cardiorespiratory fitness
- Participation in youth sports does correlate with PA in young adulthood

Taber et al. *J Phys Act Health* 2015
Kjonniksen et al. *Scan J Med Sports* 2009
Organized Sports

- 7-14 year olds: Measured PA at soccer and softball/baseball practice
  - Practice time averaged 100 minutes
- Another study found children were active 43% of the time spent at sports practice
- Overweight/obese children spend even LESS time in MVPA

Leek et al. JAMA Pediatrics 2011
PEDIATRIC TYPE 2 DIABETES
Prevalence of adolescent type 2 diabetes is increasing

- NYU: DM2 hospitalizations increased by 176% from 1997-2003 (DM1 increased by only 15%)
- Cincinnati DM clinic: 10 fold increase in DM2 from 1982-1994
- Florida DM clinic: DM2 increased from 9.4% to 20% of new cases 1994-1998
- CHOP: DM2 represented 5% of cases in 1992, now 16% in 2007
Type 2 Diabetes

- SEARCH for Diabetes in Youth study: 22% of new diabetes case among youth
  - ~15% of patients at the Eskind Pediatric Diabetes Clinic

- A highly genetic disorder but not an autoimmune disease
  - Insulin resistance
  - Beta cell failure

Impaired Fasting Glucose (IFG)
• Fasting BG $\geq 100 \text{ mg/dL}$

Impaired Glucose Tolerance (IGT)
• 2 hour BG $\geq 140 \text{ mg/dL}$

Type 2 Diabetes
• A1C $\geq 6.5\%$
  OR
• Fasting BG $\geq 126 \text{ mg/dL}$
  OR
• Random BG $\geq 200 \text{ mg/dL}$

If asymptomatic, repeat on a separate day to confirm the diagnosis of T2D
Who Will Develop T2D?
Impaired Glucose Tolerance: Insulin Resistance PLUS Insulin Insufficiency
117 obese teens

33 IGT

10 IGT

15 NGT

8 IGT

76 NGT

8 T2D

2 years

- T2D risk factors: Severe obesity, IGT and African American race
- Continued weight gain predicted progression from IGT → T2D

Yale Bright Bodies

- Weight loss clinical trial
- Monitored patients for glucose intolerance for 2 years
  - If BMI increased $<1 \text{ kg/m}^2 \rightarrow$ reverted to normal glucose tolerance
  - If BMI increased $>3 \text{ kg/m}^2 \rightarrow$ progressed to type 2 diabetes

Savoye et al. *JAMA* 2007
Incidence of Type 2 Diabetes Mellitus by 5-Year Age Groups, Sex, and Race/Ethnicity, 2002-2003

The Writing Group for the SEARCH for Diabetes in Youth Study Group,  JAMA 2007;297:2716-2724.
How should we treat IGT?

Diabetes Prevention Program

- LIFESTYLE: 58% risk reduction
  - (reduced effectiveness in children?)
- METFORMIN: 31% risk reduction

NEJM 2002
Mortality in youth with Type 2 diabetes

Patients with T2D are 66% more likely to die than patients with T1D

Waernbaum et al. *Diabetologia* 2006
Standardized Mortality Ratio is Inversely Correlated with Age at Diagnosis

Abdulghani H. Al-Saeed et al. Dia Care 2016;39:823-829
Youth with T2D have increased rates of diabetes complications compared with T1D.

- Retinopathy
- Neuropathy
- Nephropathy
- Dialysis, Blindness, Amputations
  - 26% at 15 years
  - 47.9% at 20 years
Treatment trends in adolescent T2D

- Lifestyle alone 19%
- Metformin alone 29%
- Insulin alone 21%
- Metformin + Insulin 27%
- Other 3%

55% of pediatric patients are lost to follow-up in the first 2 years
Rapid Failure of Metformin Monotherapy

No. at Risk | 699 | 542 | 425 | 297 | 187 | 92

Months since Randomization

Proportion Free of Glycemic Failure

Failure rates:
- Metformin alone, 51.7%
- Metformin–rosiglitazone, 38.6%
- Metformin–lifestyle, 46.6%

Pairwise tests:
- Metformin–lifestyle vs. metformin–rosiglitazone, P=0.15
- Metformin alone vs. metformin–rosiglitazone, P=0.006
- Metformin alone vs. metformin–lifestyle, P=0.17

Failure of metformin monotherapy begins 1 year post-diagnosis
# Long-acting Insulin

<table>
<thead>
<tr>
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<th>Glargine</th>
<th>Detemir</th>
<th>Degludec</th>
<th>NPH</th>
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<tr>
<td>Onset of Action</td>
<td>1.5 hours</td>
<td>1.5 hours</td>
<td>1.5 hours</td>
<td>3 hours</td>
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<tr>
<td>Peak</td>
<td>minimal</td>
<td>minimal</td>
<td>none</td>
<td>7 hours</td>
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<tr>
<td>Duration</td>
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<td>20 hours</td>
<td>&gt;30 hours</td>
<td>14 hours</td>
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<tr>
<td>Dose frequency</td>
<td>Daily</td>
<td>Daily</td>
<td>Daily</td>
<td>BID</td>
</tr>
<tr>
<td>Price per vial</td>
<td>$$</td>
<td>$$</td>
<td>$$ (pens)</td>
<td>$</td>
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## Short-acting Insulin

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<tr>
<th></th>
<th>Rapid-acting</th>
<th>Regular</th>
<th>U-500</th>
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<tbody>
<tr>
<td><strong>Onset of Action</strong></td>
<td>15 min</td>
<td>30 min</td>
<td>30 min</td>
</tr>
<tr>
<td><strong>Peak</strong></td>
<td>1 hour</td>
<td>2.5 hours</td>
<td>3 hours</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>5 hours</td>
<td>9 hours</td>
<td>9 hours</td>
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<tr>
<td><strong>Dose frequency</strong></td>
<td>qMeal</td>
<td>2-3 times per day</td>
<td>2-3 times per day</td>
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<tr>
<td><strong>Price per vial</strong></td>
<td>$$</td>
<td>$</td>
<td>$$</td>
</tr>
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</table>
Figure 2. Approximate Pharmacokinetic Profiles of Human Insulin and Insulin Analogues.

The relative duration of action of the various forms of insulin is shown. The duration will vary widely both between and within persons.
Actions of Glucagon-Like Peptide–1
GLP-1 Receptor Agonists

Subcut. injection
- Exenatide
- Liraglutide
- Albiglutide
- Dulaglutide
- Lixisenatide

Oral
- Sitagliptin
- Saxagliptin
- Linagliptin
- Alogliptin

Mixed Meal
Intestinal GLP-1 Release
- GLP-1 (7-36) Active
- GLP-1 (9-36) Inactive
- Rapid inactivation (>80% of pool)

DPP-4
- DPP-4 inhibitor

GLP-1 actions

GLP-1 receptor agonist

Renal Clearance
Sulfonylureas
Introducing the CHAT2D Study

A clinical research study for young people with type 2 diabetes

• Sponsored by AstraZeneca

• Phase 3 Randomized Clinical Trial of Exenatide Once Weekly
  – Once weekly subcutaneous injection
Vanderbilt Center for Surgical Weight Loss

- Adolescents 15 years and above
- Criteria:
  - >100 pounds overweight
  - BMI >40 kg/m²
  - BMI >35 kg/m² with comorbidities
  and
  - Unable to achieve weight loss through medical management
QUESTIONS?