Obesity, Youth and Diabetes (DiaObesity)

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Outline of Presentation

1. Presentation, Diagnostic Criteria, Screening
2. Rates, Causes – Genes/Environment
3. Treatment
4. Co-morbidities and complications
5. Prevention

11-8/12 y/o Female Patient

T2
• Chief Complaint - urinates 2-3 times at night times 2 months
• Weight 78 kg, BMI > 95th %ile for age/gender
  • Reported 30 lb weight gain last year, recent loss
• BP – 128/83
• Menses age 10 yrs – irregular
• Pre-natal - excessive maternal weight gain, ? diabetes,
  • FH –
    • Mother from Arizona, Al/HA, + for obesity
    • Father is Non-Hispanic White, hypertension

1. Presentation, Diagnostic Criteria, Screening

• Presentation
  • T2 indolent, mild hyperglycemia, rare acidosis, no DKA
    • AA high rate of mild DKA, higher glucose/A1C, symptomatic at presentation

• Diagnostic Criteria
  • Symptoms of diabetes plus casual glucose ≥ 200 mg/dL
  • Fasting plasma glucose ≥ 126 mg/dL
  • 2-hour post-load glucose ≥ 200 mg/dL during OGTT
  • ?A1C ≥6.5%
    • Used in adults but not established in children
1. Presentation, Diagnostic Criteria, Screening

- Evidence of insulin resistance, hypertension, dyslipidemia, NASH
- Presentation during or after puberty
- T2 in first-degree relative
- Acanthosis nigricans, sleep apnea, PCOS, candidiasis

1. Screening for T2

Results of the HEALTHY Study and Pilot – Diabetes Not Found

<table>
<thead>
<tr>
<th>Measurement</th>
<th>6th grade</th>
<th>8th grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²) Mean (SD) N = 6367</td>
<td>22.4 (5.7)</td>
<td>24.3 (5.9)</td>
</tr>
<tr>
<td>BMI percentile (adjusted for age and gender)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 85</td>
<td>50.3%</td>
<td>51.0%</td>
</tr>
<tr>
<td>85-94</td>
<td>19.8%</td>
<td>19.8%</td>
</tr>
<tr>
<td>≥ 95</td>
<td>29.7%</td>
<td>29.2%</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL) Mean (SD) N = 1740</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 100</td>
<td>93.4 (6.7)</td>
<td>98.2 (6.5)</td>
</tr>
<tr>
<td>100-109</td>
<td>84.0%</td>
<td>59.5%</td>
</tr>
<tr>
<td>110-125</td>
<td>14.7%</td>
<td>34.3%</td>
</tr>
<tr>
<td>≥ 126</td>
<td>1.2%</td>
<td>5.8%</td>
</tr>
</tbody>
</table>

* n=6 of which only 1 confirmed on follow-up testing; ** n=7

1. Associated with Overweight and Obesity

- Dyslipidemia
  - Low HDL
  - Any lipid abnormality - 12%-17%
- Elevated BP
  - 7%-16% with BP >95th percentile BP
  - 3.26 RR for HTN
- Metabolic Syndrome
  - Overall rate in US 12-19 year old – 4.2%
  - BMI > 40, 50% have MS
- Acanthosis nigricans
  - African American youth - 51%
  - Caucasians - 8%
- Earlier onset of pubarche and thelarche
  - Not earlier gonadarche
- Hyperandrogenemia and polycystic ovary syndrome

ADA\AAP Consensus Statement 2000

- Criteria*: Overweight (BMI> 85th %ile for age and sex, wt for ht > 85th %ile, or wt > 120% of ideal for ht)
- PLUS: any two of the following risk factors:
  - Family history of DM 2 in 1st or 2nd degree relative
  - Race/Ethnicity
  - Signs of insulin resistance
- Age of Initiation: age 10 or at onset of puberty
- Frequency: every two years in the context of health visit
- Test: Fasting plasma glucose preferred

* Clinical judgement should be used
1. Associated with Overweight and Obesity

- Glomerulosclerosis
  - 10-fold increase in adults, rate in children not known
- Obstructive sleep apnea
  - Six-fold increase
  - OSA independently related to HTN, CVD, behavioral disorders, poor school performance, poor quality of life
- Non-alcoholic fatty liver disease (NAFLD)
  - 10-25% elevated transaminases
  - Abdominal sonography detects fatty liver in 52%
  - Hispanic children - higher incidence
  - Rare - increasing fibrosis and eventual cirrhosis
- Gallstones
  - 2%
- Orthopedic
  - Slipped capital femoral epiphysis, genu valga, tibia vara (Blount disease), scoliosis, and osteoarthritis
- Pseudotumor cerebri
  - 15-fold increase

2. Causes T2 - THE HEALTHY MIDDLE SCHOOL STUDY

6th grade students – predominately minority students

<table>
<thead>
<tr>
<th>Distribution of Glycemic Risk Factors by BMI Percentile</th>
<th>&lt; 85 (N=3221)</th>
<th>85 - 94 (N=1255)</th>
<th>≥ 95 (N=1882)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose (mg/dL)†</td>
<td>92.8 (6.7)</td>
<td>93.3 (6.8)</td>
<td>94.5 (6.6)</td>
</tr>
<tr>
<td>Fasting glucose ≥ 100</td>
<td>13.5%</td>
<td>15.5%</td>
<td>20.8%</td>
</tr>
<tr>
<td>p &lt; .0001§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting insulin (μU/mL)†</td>
<td>8.4 (5.2)</td>
<td>12.8 (7.5)</td>
<td>22.1 (15.8)</td>
</tr>
<tr>
<td>Fasting insulin ≥ 30</td>
<td>0.8%</td>
<td>3.0%</td>
<td>19.6%</td>
</tr>
</tbody>
</table>

2. Causes – Genes and the Environment

- 3-5% increase in T1 consistently
- T2 from <2% to 25% of new onset diabetes

2. Causes – T2

- NGT
  - N = 76 (90.5%)
- IGT
  - N = 8 (8.5%)
- T2DM
  - N = 8 (9.5%)

*Mean follow-up of 20.4 ± 10.3 months

Figure 1 – Baseline and outcome glucose tolerance classification T2DM, type 2 diabetes.
2. Causes T2 - Progression from pre-diabetes to diabetes

<table>
<thead>
<tr>
<th></th>
<th>IGT to NGT</th>
<th>IGT to T2D</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>33</td>
<td>44</td>
</tr>
<tr>
<td>BMI z-score</td>
<td>2.27</td>
<td>2.76</td>
</tr>
<tr>
<td>Weight Δ kg</td>
<td>6.1</td>
<td>27</td>
</tr>
<tr>
<td>BMI Δ</td>
<td>1.06</td>
<td>6.8</td>
</tr>
</tbody>
</table>

- Weiss, et al, Diabetes Care, 28:962 2005

2. Causes T2 - Gestational Diabetes As A Driver of T2

Diabetes in pregnancy can lead to a cycle of diabetes affecting future generations. (Diabetologia. 1998;41:904-10)

11 8/12 y/o Female Patient

- Obtain the following work up:
  - Random plasma glucose 247 mg/dL, Repeat A1C 8.5%
  - CO2 20 meq/L, venous pH 7.38, LDL 178 mg/dL, Triglycerides 215 mg/dL
  - ANTIBODIES ALL NEGATIVE
  - Treatment - In or outpatient?
    - Do you start insulin?
    - Metformin alone is first line therapy when glucose level is < 250 mg/dL and patient is non-ketotic
  - All patients and families receive diabetes and lifestyle education
3. Treatment

Early and persistent glucose control is important

- Glucose monitoring
  - Self-monitoring Glucose, Understanding Glucose Targets, A1C Quarterly
- Medications
  - Glucose Lowering Agents
    - Metformin, Insulin therapy, ? Other agents
  - Others Not Approved
- Medical Nutrition Therapy
  - Weight Reduction, Lifestyle Counseling
- Psychosocial Support
  - Assess, Treat Co-morbidities, Complications
  - BP, Cholesterol, Disordered Eating, PCOS, NASH, Microalbuminuria, Eye Exams
- Visits to Health Care Team
  - Routine Pediatric Care, Flu Shots, Hep B Immunization, Transition Planning
- Sick Day Management

3. Treatment - Diabetes is Hard to Manage

Early and persistent glucose control is important

<table>
<thead>
<tr>
<th>Age</th>
<th>Pre-Meal BG</th>
<th>HS/Night BG</th>
<th>A1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toddler (0-5 yrs)</td>
<td>100-180</td>
<td>110-200</td>
<td>≥7.5 &amp; ≤8.5%</td>
</tr>
<tr>
<td>School-age (6-11 yrs)</td>
<td>90-180</td>
<td>100-180</td>
<td>&lt;8%</td>
</tr>
<tr>
<td>Adolescent (12-19 yrs)</td>
<td>90-130</td>
<td>90-150</td>
<td>&lt;7.5%</td>
</tr>
<tr>
<td>Type 2</td>
<td>80-130</td>
<td>90-150</td>
<td>&lt;7.0%</td>
</tr>
</tbody>
</table>

New onset diabetes BMI > 85th percentile

- Consider MODY – If not obese, NHW
- Pancreatic autoantibodies
- Type 1
- BG > 250 Ketones, Acidosis
- Negative
- Likely type 2
- Education, Lifestyle

- Insulin, Metformin at Dx or after Ab test
- At goal, wean insulin, metformin alone
- Not at goal, add other agents over time?

3. Treatment - Determining diabetes type in youth with BMI > 85th percentile and Treatment

- At treatment failure: Standardized approach to insulin initiation
- Primary outcome: time to failed glycemic control

- Randomized clinical trial with a pre-randomization run-in period
  - 704 patients at 15 clinical centers
  - 3 treatment regimens
    - Metformin + Placebo
    - Metformin + Rosiglitazone
    - Metformin + Intensive Lifestyle Program
  - Inclusion criteria
    - Age 10 to 17 years
    - Duration of diabetes < 2 years
    - BMI ≥ 85th percentile

Funded by National Institute of Diabetes and Digestive and Kidney Diseases National Institutes of Health
### Medics at Presentation
- No medication: 11%
- Insulin only: 12%
- Metformin only: 49%
- Metformin + Insulin: 25%
- Other medication: 4%
- 26% hypertension
- 56% dyslipidemia
- 50% depression

### Table

| Age (years) | 14.3 ± 2.0 |
| Race/Ethnicity | |
| White | 19.6% |
| African American | 37.4% |
| Hispanic | 32.2% |
| Native American | 5.5% |
| Other/Unknown | 5.3% |
| BMI (kg/m²) | 36.2 ± 7.9 |
| BMI Z-score | +2.3 ± 0.5 |

### The Study Results
- At the time of treatment failure, patients began basal insulin
- Half of the subjects failed and needed insulin treatment
- Of those on insulin, most could not be treated with basal alone
  - They progressed to MDI or insulin pumps
  - In my center, half of those on insulin used insulin pump therapy

### Funding
Funded by the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.
4. Co-morbidities and complications - Australia

<table>
<thead>
<tr>
<th>Type 1 Diabetes</th>
<th>Type 2 Diabetes</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>x</td>
<td>1.433</td>
<td>0.02</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>17.7 (13.9-17.7)</td>
<td>15.3 (6.4-14.5)</td>
</tr>
<tr>
<td>SD of diagnosis</td>
<td>4.1 (4.2-4.0)</td>
<td>3.7 (4.6-5.0)</td>
</tr>
<tr>
<td>Fasting Glucose</td>
<td>123 (106-130)</td>
<td>123 (106-130)</td>
</tr>
<tr>
<td>2H GLU (%)</td>
<td>5.7 (5.6-5.7)</td>
<td>5.1 (5.0-5.8)</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>79 (73-85)</td>
<td>71 (67-83)</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>64 (59-70)</td>
<td>60 (53-67)</td>
</tr>
<tr>
<td>waist MetS (%)</td>
<td>113 (95-118)</td>
<td>107 (96-112)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.3 (27.9-32.7)</td>
<td>22.6 (20.6-24.0)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.3 (5.8-6.7)</td>
<td>7.1 (6.5-8.0)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>241 (221-261)</td>
<td>210 (181-240)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>47 (40-54)</td>
<td>47 (40-54)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>157 (136-184)</td>
<td>210 (204-215)</td>
</tr>
</tbody>
</table>

4. Co-morbidities and complications - SEARCH Trial

68% AI, 37% Asian, 32% AA, 35% Hispanics, 16% Whites (p=0.0001)

At least 2 risk factors
92% of type 2
14% of type 1 (p<0.0001)

Rodriguez et al, Diabetes Care, 2006

4. Complications – T2

Type 2 Diabetes is a Severe Disease

- Hyperglycemic Hyperosmolar Non-Ketotic Syndrome – at onset –very high glucose levels
  - Mortality 14.3%
  - Currently 28 reported other cases
  - Mortality 43%
- Pima Indians - diagnosed < 20 years of age
  - 22% had microalbuminuria at diagnosis
  - Increased to 60% at 20-29 years of age
- Indigenous Canadians - age 23 yrs, 9 yrs duration
  - HbA1c 10.9%
  - 67% poor glycemic control
  - 45% hypertension requiring treatment
  - 35% microalbuminuria (6% required dialysis)
  - 38% pregnancy loss
  - 9% mortality


5. Prevention

Socio-ecological Model

Home Communities Health Care Access, Adherence Schools and Child Care Worksites
Age, Sex, SES, Race/Ethnicity Culture Psychosocial Factors - Stress Genes, Gene-Environment Interactions Intrauterine Environment

Socio-ecological Model

Social Norms Subculture Sectors of Influence Behavioral Settings Individual Factors

Energy Balance Obesity Insulin resistance/deficiency Type 2 Diabetes

Energy Intake Energy Expenditure

Food & Beverage Impulse Physical Activity

Built Environment Government Public Health Agriculture Education Media Land Use and Transportation Communities Foundations Industry Food Beverage Retail Leisure and Recreation Entertainment
5. Prevention
The HEALTHY Study

School unit of randomization

Primary outcome: Combined prevalence of overweight plus obesity

42 schools
≥ 50% minority &/or ≥ 50% with free/reduced lunch

Comprehensive health screening, results sent to parents

- Intervention Schools
  - Environmental changes Food service, PE
  - Behavior change - curriculum based
  - Communications and promotional campaign

Exercise Dose and Diabetes Risk in Overweight and Obese Children
Davis et al JAMA 2012

- 222 subjects
  - 2003-07
  - 15 public schools in Georgia

Random assignment
  - Low-dose (20 min/d, n= 71)
  - High-dose (40 min/d, n=73)
  - Control n=78

A Trial of Sugar-free or Sugar-sweetened Beverages and Body Weight in Children
de Ruyter et al

- 18 month trial
- 641 normal-weight children
  - 4y 10m – 11y 11m
- Random assignment to 250 ml sugar-free or sugar-containing at school
- 18 month, 26% stopped taking
- BMI z-score increased by 0.06 SD units in sugar-free group and 0.12 SD in sugar-containing group (p=0.06)
The Maps of LA County - Highest rates of Fast Food Restaurants and Convenience Stores in Areas with Greatest Obesity, 2005

- Retail Food Environment Index (RFEI)
- Red 6X> than Beige
- Obesity Rates

Source: 2005 California Health Interview Survey
Susan Babey, PhD, UCLA Center for Health Policy Research

Environmental Strategies
- Candy at the Cash Register – A Risk for Obesity and Chronic Disease
  Cohen and Babey, Rand, NEJM
- Goods placed in prominent end-of-aisle locations account for 30% of supermarket sales
- Sales of those items increases 5-fold
- Improve the hospital environment
  - Vending, gift shops, patient food, employee foods, cafeterias

5. Prevention RWJ F as in Fat

- All foods and beverages served in schools meet Dietary Guidelines for Americans.
- Increasing access to high-quality, affordable foods through new or improved grocery stores & healthier corner stores and bodegas.
- Increasing the time, intensity, & duration of physical activity during the school day.
- Reducing youths’ exposure to the marketing of unhealthy foods through regulation, policy, and effective industry self-regulation.

California
11th Lowest % of Obese Adults
28th Highest % of Obese and Overweight Children
- Provide healthy foods and beverages in schools -
  - Banned sodas
- Increase healthy foods in all communities -
  - Banned transfats, menu labeling, no fast food restaurants
  - Physical activity at school -
    - Regs amount minutes, class size
- Improve access to safe and healthy places to live, work, learn, and play
- Zoning changes, public transit funded, walking communities
- Encourage employers to provide workplace wellness programs
  - Implemented for state/county employees
  - Revamp food assistance programs
  - Healthy hospital initiative
Population Approaches to Improve Diet, Physical Activity and Smoking Habits: A Scientific Statement from the American Heart Association

Mozaffarian, et al; Circulation on line August 20, 2012

**Conclusion**

- Genetic predisposition & environmental trigger of obesity, insulin resistance and deficiency
  - Common in 1st, 2nd relatives
  - Screening criteria but rare to find asymptomatic
  - Presentation slow, mild but not always, and maybe less than thought
  - Treatment needs to be more aggressive than monotherapy to maintain glycemic control
    - Likely require basal/bolus insulin therapy
  - Complications common, early, co-morbidities related to insulin resistance
  - Prevention addresses the environment to support healthy lifestyle adoption

**Type 2 diabetes**

- DNA
- Food
- Pancreas
- Gut
- Muscle
- Insulin
- Glucose