The Road to Insulin Resistance in Childhood Obesity

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11/17/10

The Epidemic of Childhood Obesity

Science 2005

Prevalence of Childhood Obesity 1963-2004

Body Mass Index for Age at or Above the 85th and 95th Percentile by Race/Ethnicity in 1999-2006

Overweight BMI >85th

Obese BMI >95th

Health Consequences of Childhood Obesity

Overweight and obese people are at increased risk for the following:

- Type 2 diabetes
- Fatty Liver (NAFLD)
- Depression
- High cholesterol
- Heart disease
- Premature death
- Stroke
- Hypertension
- Asthma
- Some cancers

Adapted from: USSDHHS. The Surgeon General’s Call to Action to Prevent and Decrease Overweight and Obesity, 2001.

Why Me?

DIABETES ARE YOU AT RISK?
Incidence of T1 and T2 DM by 5-year Age groups, Sex and Race, 2002-2003 The SEARCH Study

T 1 DM

T 2 DM

Risk Factors For T2DM in Youth
- Obesity (Insulin Resistance/Hyperinsulinemia)
- Puberty
- Ethnicity
- Gender (F>M)
- Family History
- Maternal Diabetes
- Sedentary Lifestyle

Metabolic and Clinical Profile of Obese Adolescent with T2DM
- Gender Female
- Age 13 yrs
- BMI 31 (<95th)
- Fasting Glucose 98 mg/dl
- 2Hr Glucose 220 mg/dl
- Fasting Insulin 60 uU/ml
- Fasting C-pep 3.8 ng/ml
- Triglyceride 208 mg/dl
- A1C 6.8%

Marked Acanthosis Nigricans

The Natural History of Type 2 Diabetes in Adults

Normal Glucose Glucose
↓
Impaired Glucose Tolerance
↓
Type 2 Diabetes

Is This Pattern the same in Children?

In a multiethnic cohort of 500 obese children and adolescents we determined:

- the prevalence of IGT and the Metabolic Syndrome
- surrogate markers of insulin resistance

Prevalence of Impaired Glucose Tolerance in Obese Children and Adolescents

Sinha R et al NEJM 2002; Weiss R et al NEJM, 2004
Effect of the Degree of Obesity on the Prevalence of the Metabolic Syndrome in Obese Youth

Weiss et al, NEJM 2004

Trends in Components of the Metabolic Syndrome Across Weight Categories

P for all trends <0.0001, adjusted for gender, puberty and ethnicity

Insulin Resistance: Definition

A condition in which greater than normal amounts of insulin are required to produce a normal biological response.

Olefsky JM In : Ellenberg and Rifkin's Diabetes Mellitus 5th edition 1997

Fatty Acid Overload Hypothesis

What Causes Muscle Insulin Resistance?

• Abnormal Fat Distribution/Metabolism
• Cytokines (TNF-alfa, Il-6)
• Mitochondrial Dysfunction
• Oxidative Stress
• ER Stress
• Others?
Mechanisms of Insulin Resistance

Limited or Inefficient Storage of Fat in the Subcutaneous Depot

Liver

Muscle

Central Obesity

Study Paradigm

- Assessment of Insulin Sensitivity
  - The Hyperinsulinemic Euglycemic Clamp
- Assessment of Insulin Secretion
  - The Hyperglycemic Clamp
- Body Composition
  - DEXA

° H NMR Spectroscopy of the Soleus Muscle of a lean subject

MRI Determination of Visceral and Subcutaneous Lipid

Visceral Fat

Subcutaneous Fat

MRI Determination of Visceral and Subcutaneous Lipid

Visceral Fat Area: 520 cm²
Subcutaneous Fat Area: 30 cm²

Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>IGT</th>
<th>NGT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>5M / 9F</td>
<td>6M / 8F</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>6W / 3B / 5H</td>
<td>4W / 5B / 5H</td>
</tr>
<tr>
<td>Age</td>
<td>14 ± 1</td>
<td>13 ± 1</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>37 ± 1.5</td>
<td>39 ± 1.4</td>
</tr>
<tr>
<td>% Total Body Fat</td>
<td>42 ± 2</td>
<td>43 ± 1.2</td>
</tr>
<tr>
<td>Plasma Leptin (ng/ml)</td>
<td>26 ± 2</td>
<td>30 ± 4</td>
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</tbody>
</table>
Baseline and 2-hr Data from the OGTT

<table>
<thead>
<tr>
<th></th>
<th>NGT</th>
<th>IGT</th>
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</thead>
<tbody>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>90.9 ± 1.4</td>
<td>91.3 ± 3.0</td>
</tr>
<tr>
<td>2-hour glucose (mg/dl)</td>
<td>110.7 ± 4.5</td>
<td>161.8 ± 4.5 **</td>
</tr>
<tr>
<td>Fasting insulin (µU/ml)</td>
<td>32.6 ± 3.6</td>
<td>40.2 ± 6.8 **</td>
</tr>
<tr>
<td>2-hour insulin (µU/ml)</td>
<td>143.1 ± 21.0</td>
<td>503.7 ± 218.0 *</td>
</tr>
<tr>
<td>Adiponectin (µg/ml)</td>
<td>8.51 ± 0.99</td>
<td>9.12 ± 0.87 *</td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td>5.10 ± 0.08</td>
<td>5.25 ± 0.10</td>
</tr>
</tbody>
</table>

Data presented as Mean ± SE, *p<0.05, **p<0.01

Intramyocellular (IMCL) Lipid Content and Insulin Sensitivity

Central Adiposity in Obese Children
Research Design

**Subjects**
- 118 obese adolescents

**Study**
- Glucose Tolerance Test

**Imaging**
- 1H-NMR, Abdominal MRI, Liver Fat by Fast Gradient MRI

**Analysis**
- The group was stratified into tertiles based on the ratio of Visceral fat in CM2 / Visceral+Subcutaneous fat in CM2.
- Therefore, subjects in Tertile 1 have the lowest proportion of visceral fat, while those in Tertile 3 have the highest.

Taksali S et al, Diabetes 2008

Marked Differences in Visceral and Subcutaneous Abdominal Fat Despite Similar Degree of Overall Adiposity

<table>
<thead>
<tr>
<th>Tertile 1</th>
<th>Tertile 2</th>
<th>Tertile 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR 2.60</td>
<td>IR 1.17</td>
<td>IR 0.82</td>
</tr>
</tbody>
</table>

Taksali S et al Diabetes, 2008

Prevalence of the Metabolic Syndrome (percentage)

- Tertile 1: 10%
- Tertile 2: 20%
- Tertile 3: 40%

* Adjusted for age, gender, race/ethnicity

Taksali S et al Diabetes 2008
Metabolic Phenotype of a young girl with Non-Alcoholic Steatohepatitis (NASH) and T2DM

L.G.  DOB 12-10-91
- Height: 148 cm
- Weight: 58 kg
- BMI: 26.2 kg/m²
- % fat: 47% (BIA)
- ALT: 206 U/L (0-35)
- AST: 211 U/L (0-35)
- GGT: 163 U/L (7-33)
- Fasting Glucose: 154 mg/dl
- Fasting Insulin: 34 µU/ml
- Triglyceride: 254 mg/dl
- HDL-CHOL: 25 mg/dl

Liver Needle Biopsy
Severe macrovesicular steatosis
Bridging fibrosis (stage III)

Imaging Studies

- 72 Obese Adolescents
  - Liver MRI
    - Dixon method for hepatic fat quantitation
  - Abdominal MRI
    - Fat partitioning

Burgert T et al, JCEM 2006

Validation of the two Point Dixon Method (2PD) against hepatic fat content measured by ¹H-NMR in 34 obese and lean adolescents.


African-American Boy
NORMAL LIVER

Hispanic Boy
FATTY LIVER
Fatty Liver and Metabolic Pattern

Excess Fat
In The Wrong Place
Is Bad

Sensitivity of Beta Cell for C-Peptide Secretion to Glucose Stimulus

Possible Metabolic Staging of Pre-Diabetes in Childhood Obesity

Weiss R et al, Diabetes 2005
Metformin improves glycaemia in type 2 diabetic adolescents

**Metformin Placebo**

<table>
<thead>
<tr>
<th>Fasting Plasma Glucose (mmol/L)</th>
<th>Δ</th>
<th>HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>9.0</td>
<td>0.0% (p=0.001)</td>
</tr>
<tr>
<td>Placebo</td>
<td>7.0</td>
<td>1.2% (p&lt;0.001)</td>
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Hundal & Inzucchi, Drugs 2003

**Yale Pediatric Obesity/Diabetes Research Group**

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- Sylvie DuFour

**GRANTS:** NIH/NICHD, ADA

**THANK YOU!**
Natural History of Pre-Diabetes in Youth?

102 obese children and adolescents

NGT
N=71

IGT
N=31

NGT
N=10 (91.5%)

IGT
N=6 (8.5%)

T2DM
N=10 (32.3%)

Mean follow-up of 21 months

Factors Associated With Transition Between Categories of Glucose Tolerance

- Marked Weight gain (NGT to IGT or IGT to T2DM)
- Profound Insulin Resistance at Baseline
- Reduced first phase insulin secretion at baseline