Adipocytokines and Insulin Resistance in the Obese Pediatric Population

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Tasks for Today

I. Why study obesity in the pediatric population?
II. Why study the adipocyte?
   - The adipocyte and the obese state
   - Adipocyte as an endocrine organ -- adipocytokines
III. Relationship between obesity/inflammation/metabolic syndrome
IV. Childhood Predictors of Adult Type 2 Diabetes
V. Where do we go from here?

The Adipocyte
Why do we care?

Obesity in Children: Definitions

- Growth is a major component of normal pediatric development
- Height and weight should be evaluated annually
- Degree of fatness is determined by calculating Body Mass Index (BMI) = Weight (kg)/Height (m$^2$)
- BMI is then plotted on a curve to determine percentiles for age and sex
- BMI > 85th % < 95th % = overweight
- BMI ≥ 95th % = obese

Growth Curves and BMI

Why is Calculating/Plotting BMI Important in Pediatrics?

- BMI in adults is used to determine weight status (18.5 – 24.9 = normal weight)
- In children, BMI is dependent on changes in height and influence of puberty.
- Age 5: BMI = 22 (>>97th%) = obese
- Age 10: BMI = 22 (95%) = obese
- Age 13: BMI = 22 (85%) – overweight
- Age 18: BMI = 22 (50%) – normal weight

http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/
Why do we care?

**Obesity Prevalence in Pediatrics**
Lessons from WNY

Percent of children in general pediatrics practice
Overweight (BMI > 85th – 95th percentile)
Obese (BMI > 95th%) in Western New York.

![Percent of children in general pediatrics practice](http://edweb6.educ.msu.edu/kin/ResearchOutreach/BAGL/bagl_files/image002.jpg)

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**Pediatric Obesity Beyond Western New York**

- Obesity rates in adults are stabilizing (we think)
- However...
  - 710,949 patients age 2-19 years
  - 37.1% overweight
  - 19.4% obese
  - 6.4% extremely obese (BMI > 1.2x 95th%)
- Highest rates of extreme obesity in Hispanic and African American
- Obesity rates continue to increase in the pediatric population
- Obesity is occurring at a young age
  - Odds ratio of extreme obesity is 2.96 in Hispanic children age 2-5.
  - Odds ratio of extreme obesity is 1.68 (boys) and 2.46 (girls) in African American children age 2-5
  - Odds ratio of extreme obesity is 1 in non-hispanic Caucasian children age 2-5

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**Implications of Childhood Obesity**

- Among adolescents with BMI > 95th%
  - 50% will become obese adults
  - 70% will be overweight or obese

If obesity rates just remain stable, in the next 25 years, the number of Americans living with diabetes will nearly double, increasing from 23.7 million in 2009 to 44.1 million in 2034. Over the same period, spending on diabetes will triple, rising from $113 billion to $336 billion, even with no increase in the prevalence of obesity.

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**Implications of Pediatric Obesity**

- Increased risk for Type 2 diabetes, hyperlipidemia, hypertension, cardiovascular disease at younger age
- Orthopedic complications
- Exercise Intolerance
- Sleep apnea (Poor school performance)
- Elevated inflammatory markers
- Fertility issues – females – Polycystic ovarian syndrome
  - males – hypogonadism
- Socialization problems

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**Pediatric Obesity – What is the Cause?**

**Most common cause = Exogenous Obesity**

Calories consumed >> Calories Expended

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**Obesity as a Risk Factor for Disease**

Obesity/Visceral Fat Accumulation in adults is linked to:

- Insulin Resistance
- Type 2 diabetes
- Hypertension
- Hyperlipidemia
- Atherosclerosis
- Metabolic Syndrome
- Increased Cardiovascular disease

We are finding similar correlations in the pediatric population

Obesity is associated with a state of low-grade chronic inflammation

Obesity alters the metabolic activity and the secretory patterns of adipose tissue

http://edweb6.educ.msu.edu/kin/ResearchOutreach/BAGL/bagl_files/image002.jpg
The Adipocyte: Not just a Storage/Release Organ

**Glucose and Free Fatty Acid Uptake stimulated by Insulin in Fed State**

Lipolysis with release of Free Fatty Acids and glycerol in the Fasted State

**Adipocytokines**

- Adipocyte derived proteins
- Autocrine and Paracrine Effects
- Involved in:
  - Energy Balance
  - Glucose homeostasis
  - Lipid metabolism
  - Inflammation

Leptin was the first adipocytokine discovered in 1995
Paved the way for looking at adipose tissue as an endocrine organ influencing feeding and metabolism

Adapted from
http://www.biochemsoctrans.org/bst/033/1078/bst0331078f01.gif

**Adipocytokines: Leptin**

- Leptin levels correlate with BMI
- Adipocyte Mass
- Triglyceride Content
- Acts on hypothalamic receptors
  - VMN
  - Arcuate Nucleus
- Inhibits Feeding
- Stimulates thermogenesis
- Improves insulin sensitivity
- Trend towards weight loss

**Adipocytokines: Adiponectin**

- Secreted by adipose tissue
- Adiponectin
- Adiponectin levels correlate with insulin sensitivity
- Low adiponectin levels increase cardiovascular risk
- Abundant in plasma (5 – 30 μg/ml)
- Circulates as complexes
- trimers, hexamers, HMW forms (metabolically active)
- Acts on multiple tissues
- Skeletal muscle
- Liver
- At least 3 adiponectin receptors have been identified
- Improves insulin sensitivity
- Enhances insulin-signaling through IRS-1
- Activates AMP kinase
- Treatment with TZDs can increase adiponectin levels in mouse models

**Clinical Utility of Leptin**

- Rare cases of Congenital Leptin Deficiency due to mutations of leptin gene
  - Hyperphagia
  - Extreme obesity starting in early childhood
- Congenital lipodystrophy syndromes (partial due to PPARγ mutations)
  - Severe insulin resistance
  - Hyperlipidemia
- Obesity
- Leptin levels are elevated
- State of "Leptin-Resistance"
Anti-atherogenic effects of Adiponectin

Adiponectin affects atherogenesis by:
1) Inhibiting monocyte attachment
2) Attenuating vascular smooth muscle cell proliferation (inhibits MAPK)
3) Suppressing foam cell formation
4) Protecting against plaque rupture by inhibiting MMPs

Adiponectin levels are decreased in those with Coronary Artery Disease

Adipocytokines Tumor Necrosis Factor α

The link between insulin resistance/obesity and a chronic inflammatory state was made when it recognized that TNFα expression is highly induced by obesity

TNFα is secreted by both adipocytes and macrophages and lymphocytes that migrate into visceral fat
- TNFα production is increased in obese individuals
- TNFα increases adipocyte expression of MCP-1 which leads to chemotaxis of monocytes.

Adipocytokines Tumor Necrosis Factor α

Inhibitory effects of TNFα on insulin action are decreased by TZDs
1) decrease in serum TNFα
2) correlated with improved insulin sensitivity

Obesity and the Development of Insulin Resistance

- Defining insulin resistance
- Relationship of insulin resistance to low grade chronic inflammation
- Defining metabolic syndrome in children
- Can we predict who will go on to develop Type 2 Diabetes?
- What can we do to help our patients?
**Insulin Resistance and Metabolic Disease**

- Failure of target organs to respond normally to insulin action
  - Incomplete suppression of hepatic glucose output
  - Impaired glucose uptake in the periphery
- Adipose tissue
- Increased insulin requirement to maintain euglycemia
- Associated with the metabolic syndrome
  - Central obesity
  - Hypertension
  - Dyslipidemia
  - Hyperglycemia

**Signs/Tools for Measuring Insulin Resistance**

- Acanthosis Nigricans
- Fasting Insulin – Elevated in the face of normal glucose
  - Euglycemic Hyperinsulinemic Clamp – Gold Standard
  - 2 IVs – one insulin infusion, one infusing D20 – goal to maintain blood sugar at 100 mg/dL
    - Higher the dextrose rate to maintain blood sugar, the more insulin sensitive the subject
    - Can calculate glucose disposal
    - Labor/time intensive

**Tools for Measuring Insulin Resistance**

- Homeostatic Model Assessment of Insulin Resistance (HOMA-IR)
  \[ \text{HOMA-IR} = \frac{\text{fasting insulin (µU/ml)} \times \text{fasting glucose (mM)}}{22.5} \]

- Quantitative Insulin Sensitivity Check Index (QUICKI)
  \[ \text{QUICKI} = \frac{1}{\log \text{fasting glucose (mg/dL)} + \log \text{fasting insulin (µU/mL)}} \]

**HOMA-IR in Adolescents with Normal Fasting Glucose**

- Non-diabetic
- Type 2 Diabetes

**Obesity and Metabolic Disease**

- Caloric Excess/Inactivity
  - Visceral Fat Accumulation
  - Dysregulation of adipocytokine secretion (adiponectin, TNFα, IL-6, MCP-1)
- Insulin Resistance
  - Hypertension
  - Type 2 Diabetes
  - Hyperlipidemia
  - Atherosclerosis
- Inflammation
- Metabolic Syndrome

**Obesity and Inflammation**

- TNFα
  - Secreted from adipocytes harvested from obese adults
  - mRNA correlates with BMI and %body fat
- Interleukin-6
  - Secreted by infiltrating monocytes/macrophages
  - Plasma levels correlate with obesity and insulin resistance
  - Elevated levels may predict risk of T2DM
- Monocyte Chemoattractant Protein 1
  - Plasma levels correlate with BMI
  - Associated with adipocyte differentiation
  - Negatively correlates with adiponectin
- C-reactive protein
  - Correlates with BMI, fasting insulin and insulin resistance
  - Associated with atherogenic lipid profiles
- Abnormal neutrophil count
- Abnormal ferritin/transferrin ratio
Obesity and Inflammation in the Pediatric Population

- Herder et al. 2007
  - 519 adolescents (mean age 15.5 ± 0.8 yr)
  - IL-6 correlates with BMI/WC
  - HOMA-IR correlates with inflammation
- Winer et al. 2006
  - 589 obese children and adolescents
  - Adiponectin levels declined with increasing BMI
  - Adiponectin levels declined with increasing BMI
  - Inverse correlation between adiponectin and CRP
- Skinner et al 2010
  - Cross sectional analysis NHANES (1999-2006) age 1-17 yrs
  - Stratified – very obese (≥99th% BMI), obese, overweight
  - Elevated CRP noted as young as age 3-5 in very obese children
  - Abnormal neutrophil count as young age 6-8 very obese children
  - Abnormal ferritin/transferrin at age 9-11
  - Hypothesize that early elevated inflammatory markers may contribute to long term cumulative vascular damage.

Obesity and Metabolic Disease

- Visceral Fat Accumulation
  - Caloric Excess / Inactivity
  - Dysregulation of adipocytokine secretion (adiponectin , TNFα , IL-6 , MCP-1 )
- Obesity/Insulin Resistance
  - Inflammation
  - Hypertension
  - Type 2 Diabetes
  - Hypolipidemia
  - Atherosclerosis

Metabolic Syndrome

- Definition for Adults
  - NCEP ATP III (3/5 components)
    - Waist Circumference – >102 cm (men), >88 cm (women)
    - Triglyceride ≥150 mg/dL
    - HDL < 40 mg/dL (men), < 50 mg/dL (women)
    - Blood Pressure ≥130/≥85 mm Hg
    - Fasting glucose ≥110 mg/dL
  - IDF (Central obesity + 2/4 components)
    - Central Obesity = elevated waist circumference
    - Triglyceride ≥150 mg/dL or on lipid lowering drug
    - Low HDL or being treated for low HDL
    - Elevated BP or being treated for hypertension
    - Fasting glucose ≥100 mg/dL or Diagnosis of Type 2 Diabetes

Defining Metabolic Syndrome

- Definitions for Pediatrics
  - At least 4 Different Definitions
    - 3/5 components (similar to adults)
      - BMI ≥2SDs or WC ≥90th%
      - Blood pressure ≥90th/95th%
      - Triglycerides: ≥90th% or ≥110 mg/dL
      - HDL ≤ 5th%/10th% or ≤40 mg/dL
      - FBS ≥100/110 mg/dL or Impaired glucose tolerance
  - Affects ~30% obese children/adolescents

Metabolic Syndrome in Children

- Lee and colleagues, 2008 J Pediatrics
  - Compared definitions of pediatric metabolic syndrome
  - 251 children and adolescents
  - Prevalence of Metabolic Syndrome (3 components)
    - Weiss et al – 18.7%
    - Cook et al. – 21%
    - Ford et al. – 25%
    - Cruz et al. – 13%
  - Average Prevalence of MS (all definitions) by race and obesity
    - 31% – overweight AA, 0.7% non-overweight AA
    - 43% – overweight Caucasians, 2.8% non-overweight Caucasians
    - Youth with MS are older, heavier, and have greater WC
    - Correlated strongly with higher fasting insulin levels
    - Negative correlation with plasma adiponectin levels

Conclusions (Lee et al.)

- Definition of Metabolic Syndrome in children should include an obesity component
  - Either BMI or WC
  - Similar to IDF in adults
  - Regardless of definition, Metabolic syndrome associated with
    - Elevated fasting insulin
    - Low adiponectin
    - Fasting insulin and/or adiponectin may serve as surrogate markers for metabolic syndrome.
  - Identified racial differences in inflammatory mediators assoc with MS – needs to be explored

Weiss et al. 2004; Cook et al. 2003; Ford et al. 2006; Cruz et al. 2004.
Metabolic Syndrome in Children: WCHOB experience

<table>
<thead>
<tr>
<th></th>
<th>Study (n=26)</th>
<th>Control (n=13)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>34.9±6.9</td>
<td>20±2.4</td>
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<tr>
<td>BMI Z-score</td>
<td>2.3±0.4</td>
<td>-0.1±0.85</td>
<td>&lt;0.001*</td>
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<td>Waist Circ (cm)</td>
<td>112.6±17.6</td>
<td>71.4±6.5</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>WC &gt;90% for age, sex</td>
<td>23/26</td>
<td>0/13</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Elevated SBP</td>
<td>11/26</td>
<td>0/13</td>
<td>0.03</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>36.8±8.2</td>
<td>51.8±15.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>106.1±47.9</td>
<td>55.9±26.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Insulin (U/L)</td>
<td>16 (12,24.5)</td>
<td>5 (4,8.5)</td>
<td>0.001</td>
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<tr>
<td>HOMA-IR</td>
<td>4.7±3.5</td>
<td>1.2±0.6</td>
<td>0.001</td>
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<tr>
<td>Met. Syndrome</td>
<td>6/26 (23%)</td>
<td>0/13 (0%)</td>
<td>0.076</td>
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</table>

Obesity and Adipocytokines

Model for Disease Prevention

Identifying Predictors for Development of Type 2 Diabetes in Pediatric Population

Longitudinal Prospective Cohort Studies – No interventions in either trial (Morrison et al. 2010 Arch Pediatr Adolesc Med)

Princeton Follow-up Study
- Multistage survey of cardiovascular risk factors in childhood
- 882 subjects enrolled grades 1-12 (average age 12.4 years; 28% black)
- Followed for 26 years

National Growth and Health Study
- Designed to look at racial disparities in CV in females
- 1067 subjects enrolled at age 10 (53% black)
- Followed for 9 years

Both studies:
- BMI, BP, Parental diabetes diagnosis – baseline
- PFS – Fasting glucose, lipid profile at baseline and follow-up
- NGHS – Fasting glucose/insulin lipid profile baseline, age 15, age 19

At follow-up – subjects asked whether they were diagnosed with diabetes or took medications for diabetes.

Identify predictors for IGT/T2DM

Development of Diabetes in Prospective Cohorts

- Princeton Follow-up Study
  - Incidence of T2DM at mean age 39
    - 40/822 (4.9%)
    - 9.9% in black women, 4% in white women
    - 4.7% in black men, 3.4% in white men
    - Excluded those on insulin exclusively – could not rule out T1DM

- NGHS Study
  - Incidence of T2DM at mean age 19
    - 8/1069 (0.75%)
    - 1.2% in black women, 0.2% in white women

Predictors of development of Type 2 diabetes in Pediatric Population

- Princeton Follow-up Study
  - Factors at start of study that predict likelihood of diabetes 22-30 years later
    - BMI ≥ 95th%
    - SBP >95th%
    - Parental DM diagnosis
    - FBS ≥ 100 mg/dL
    - Black Race

If BMI, SBP, and DBP <75th% and No Parental DM
Risk of Diabetes is 1%
Predictors of development of Type 2 diabetes in Pediatric Population

- **NGHS Study**
  - Factors at baseline predicting likelihood of diabetes 9 years later
    - SBP ≥ 95th%
    - Parental DM diagnosis
    - Fasting insulin ≥ 95th% (risk 12x)**
    - HDL < 5th%
  - Follow-up study at 14 years (Morrison et al. 2010 in press, Metabolism Clinical and Experimental)
    - BMI Change = obesity acceleration (top quartile, risk 3.05x)
    - Metabolic syndrome at age 10 years (4%; risk 2.72x)
    - Fasting insulin (top quartile, risk 2.17x)

If BMI, SBP, and DBP <75th% and No Parental DM
Risk of Diabetes is 0.2%

What these prospective studies teach us?

- History and physical at the primary care level is useful for predicting those at risk
- Basic fasting laboratory work can aid in focusing risk
  - Follow AAP guidelines for screening
  - Fasting lipid profile, glucose, insulin
  - Other measures of insulin resistance
- Family history is a strong predictor
- Can identify those at low risk
- Can identify those at high risk – target for interventions/referral

What therapies do we have to offer?

1) Lifestyle/Behavioral Modification Interventions
2) Pharmacotherapy*
3) Bariatric Surgery*

Lifestyle/Behavioral Modification

- Education is Key
  - Dietary counseling
  - Exercise programs
- Give guidelines for weight loss
- Enroll in behavioral weight loss programs
- "Shift" the environment
- Engage the family

Meta-Analysis of Treatments for Childhood Obesity

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Standardized mean difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(None FDA approved for kids)</td>
<td>-1.01</td>
<td>(-1.28, -0.73)</td>
</tr>
<tr>
<td>Orlistat</td>
<td>-0.29</td>
<td>(-0.46, -0.12)</td>
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<tr>
<td>Metformin</td>
<td>-0.17</td>
<td>(-0.62, 0.28)</td>
</tr>
<tr>
<td>Dietary</td>
<td>-0.22</td>
<td>(-0.56, 0.11)</td>
</tr>
<tr>
<td>Physical Activity</td>
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<td></td>
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<tr>
<td>Effect on BMI</td>
<td>-0.02</td>
<td>(-0.21, 0.18)</td>
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<tr>
<td>Effect on Fat Mass</td>
<td>-0.52</td>
<td>(-0.73, -0.30)</td>
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<tr>
<td>Combined Lifestyle</td>
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<td></td>
</tr>
<tr>
<td>Targeting Family</td>
<td>-0.84</td>
<td>(-0.88, -0.39)</td>
</tr>
<tr>
<td>Targeting Children</td>
<td>-0.17</td>
<td>(-0.40, 0.05)</td>
</tr>
</tbody>
</table>

McGovern et al. 2008 JCEM
76 eligible trials – 61 included in the analysis
Negative SMD favors intervention
Conclusions

- The adipocyte serves as a fuel reservoir and an endocrine organ
- Low grade chronic inflammation is an aspect of the obese state
- Obesity is associated with insulin resistance and the metabolic syndrome
- History and physical exam findings can identify those at highest risk for developing T2DM
- Programs which focus on families and target diet and lifestyle have the greatest likelihood of success in treating obesity
- Goal is to identify safe, sustainable programs for obesity management

What can we do as pediatricians?

- Calculate and plot BMI at each well-child and/or sick visit
- Identify patients at high risk for developing obesity
  - Ethnicity
  - Family history
  - Rapid Weight Gain
- Speak with families about the diagnosis
- Educate about long-term consequences
- Provide information about community-based programs to address nutrition/exercise
- Screen for complications (AAP guidelines)