Metabolic Alterations in Children with Obstructive Sleep Apnea

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Disclosures: None
Metabolic Alterations in OSA: Study Overview

Obesity

Hypertension
Dyslipidemia
Hyperinsulemia
Abdominal Obesity

Obstructive Sleep Apnea

Metabolic Syndrome

Adults
Children

Cardiovascular Disease
Introduction

- Childhood Obesity

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Year 1</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-11 years</td>
<td>1980</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>2012</td>
<td>18%</td>
</tr>
<tr>
<td>12–19 years</td>
<td>1980</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>2012</td>
<td>21%</td>
</tr>
</tbody>
</table>

CDC, Atlanta
Introduction

- Annual medical cost of obesity in the U.S.
  - 2008 - $147 Billion
  - 2012 - $190.2 Billion
  - 21% Annual medical spending
  - Childhood obesity medical cost: $14 billion

*Cawley et al, 2012*
*Marder et al, 2009*
Introduction

- OSA – Disorder of breathing during sleep
  
  Characterized by upper airway collapse that disrupts normal respiratory gas exchange or causes sleep fragmentation.
  
  (Tripuraneni et al, 2013)

- Prevalence of OSA in prepubertal children – 12-14%
  
  (Bhushan et al, 2011; Gozal et al, 2008)

- Prevalence of OSA in obese children – 34-36%
  
  (Canapari et al, 2011)
Introduction

- Risk of developing OSA is 4-5 times higher in obese compared to non-obese children
  (Tripuraneni et al, 2013; Canapari et al, 2011)

- Prevalence of Metabolic syndrome
  - Adults 20%
  - Children 8-10%

(Ferranti et al, 2004)
Literature:

Severity of OSA is linked with Metabolic Alterations

- De La Eva RC, 2002 (Children + adolescents)
- Redline S, 2007 (Adolescents)
- Verhulst SL, 2007 (Children)
- Hannon TS, 2011 (Adolescents)

Obesity is linked with Metabolic Alterations

- Arens R, 2011 (Children)
- Kaditis AG, 2005 (Children + adolescents)
- Tauman R, 2005 (Children)
- Nakra N, 2008 (Children + adolescents)
Direct comparisons of these studies are difficult because of:

- Different Inclusion/Exclusion Criteria
- Differences in overall duration and severity of OSA
- Different cut-off values for the AHI used to define OSA
Metabolic Alterations in OSA

**Hypothesis:**
Variations in the components of Metabolic Syndrome (dyslipidemia and insulin resistance) are associated with OSA in young children independent of their BMI z Score.

**Objectives:**
- Compare differences in metabolic variables and insulin resistance among patients with or without OSA
- To determine if alterations in metabolic variables and insulin resistance in patients with OSA occur independent of their BMI z Score
Metabolic Variables in OSA: Methods

Setting/IRB: Ann & Robert H Lurie Children’s Hospital
Pediatric Specialty
Tertiary Care Medical Center

Time line: January, 2010 - December, 2013
Metabolic Variables in OSA: Methods

Total identified: 144

Inclusion Criteria: (n=76)

- Age 2-12 years
- Overnight polysomnography
- Height and Weight (BMI)
- Metabolic Lab Data
  - Lipid panel
  - Glucose
  - Insulin
  - Blood Pressure
Exclusion Criteria (n=68)

- Receiving CPAP (n=4)
- Genetic Abnormalities (n=11)
- Craniofacial Anomalies (n=2)
- Organ Transplant Recipients (n=8)
- Diabetics (n=11)
- Multiple Medical Problems (n=6)
- Patients with incomplete or no information on glucose and insulin (n=21)
- Lipid Lowering Meds (n=5)
Metabolic Variables in OSA: Methods

- Polysomnography: Standard overnight hospital based

- Routine lab tests: Lipid Profile, Blood Glucose level, Insulin level

- BMI z score Calculation: Growth standards, Online software (Epiinfo) www.cdc.gov
Metabolic Variables in OSA: Methods

- Homeostasis Model Assessment (HOMA) calculation:
  \[
  \text{HOMA} = \frac{\text{Fasting Insulin (µIU/mL)} \times \text{Fasting blood glucose (mmol/L)}}{22.5}
  \]
  (Matthews et al, 1985)

- Insulin resistance (HOMA-IR):
  Gender Specific pre-pubertal cut-offs (Kurtoglu et al, 2010)
  - Boys >2.67
  - Girls >2.22
Metabolic Variables in OSA: Definitions

*Obesity*: BMI z score > 95\textsuperscript{th} percentile

*OSA*: Mild: AHI between 1 and 4.99/hour
Moderate: AHI between 5 and 9.99/hour
Severe OSA: AHI ≥ 10/hour

No OSA: AHI < 1/hour
Results: Description of Patient Population

- **Age:** $8.1 \pm 2.5$ (range, 2.4-11.9 years)
- **BMI z score:** $2.8 \pm 0.75$ (range, 1.7-6.3)
- **Obese:** (100%)

Total = 76

- **M:** 43 (56.6%)
- **F:** 38 (39.2%)
# Results: Profile of Age and BMI z Score of Patients Included in the Study

<table>
<thead>
<tr>
<th>Variables</th>
<th>No OSA (n=22)</th>
<th>Mild OSA (n=27)</th>
<th>Moderate OSA (n=12)</th>
<th>Severe OSA (n=15)</th>
<th>Overall p value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>8.0 ± 2.1</td>
<td>8.6 ± 2.6</td>
<td>8.6 ± 3.1</td>
<td>7.7 ± 2.6</td>
<td>0.68</td>
</tr>
<tr>
<td>BMI z Score</td>
<td>2.7 ± 0.8</td>
<td>2.7 ± 0.5</td>
<td>2.8 ± 1.2</td>
<td>2.8 ± 0.6</td>
<td>0.96</td>
</tr>
</tbody>
</table>
Results: The Relationship between Metabolic Variables and Worsening OSA

- **No Significance (ANOVA)**
  - Total cholesterol (p=0.14)
  - Triglycerides (p=0.86)
  - HDL-C (p=0.99)
  - LDL-C (p=0.13)
  - Diastolic Blood Pressure (p=0.33)
  - Systolic Blood Pressure (p=0.12)
Results: The Relationship between Fasting Insulin, and worsening OSA

\[ p < 0.01 \]
Results: The Relationship between Blood Glucose and worsening OSA

\[ p < 0.01 \]
Results: The Relationship between HOMA-IR and worsening OSA

$p<0.01$
Results: Correlation Analysis Demonstrating the Relationship of AHI to Fasting insulin and HOMA
Results: Linear Regression Analysis Showing Relationship of a Number of Variables to Fasting Insulin and HOMA-IR

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>β (Standardized coefficient)</th>
<th>p value</th>
<th>β (Standardized coefficient)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fasting Insulin. Adjusted $r^2 = 0.07$, $p=0.10$</td>
<td></td>
<td>HOMA-IR. Adjusted $r^2 = 0.08$, $p=0.08$</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.05</td>
<td>0.10</td>
<td>0.05</td>
<td>0.15</td>
</tr>
<tr>
<td>Gender</td>
<td>-0.11</td>
<td>0.45</td>
<td>-0.13</td>
<td>0.43</td>
</tr>
<tr>
<td>TST (hours)</td>
<td>-0.03</td>
<td>0.65</td>
<td>-0.06</td>
<td>0.43</td>
</tr>
<tr>
<td>BMI z Score</td>
<td>0.13</td>
<td>0.17</td>
<td>0.14</td>
<td>0.19</td>
</tr>
<tr>
<td>AHI (/hour)</td>
<td>0.02</td>
<td><strong>0.04</strong></td>
<td>0.02</td>
<td><strong>0.03</strong></td>
</tr>
</tbody>
</table>
## Results: Multinomial Logistic Regression Analysis of the Effect Of Moderate and Severe OSA on Elevations in Fasting Insulin and HOMA-IR Independent of BMI z Score

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>β Coefficient</th>
<th>p Value</th>
<th>O.R.</th>
</tr>
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<tr>
<td>Pseudo R² (Snell &amp; Cox) = .318, <em>p</em>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Moderate OSA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.06</td>
<td>0.73</td>
<td>1.10</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>-0.90</td>
<td>0.31</td>
<td>0.41</td>
</tr>
<tr>
<td>BMI z Score</td>
<td>0.02</td>
<td>0.97</td>
<td>1.01</td>
</tr>
<tr>
<td>Fasting Insulin</td>
<td>0.10</td>
<td>0.05</td>
<td>1.10</td>
</tr>
<tr>
<td>Pseudo R² (Snell &amp; Cox) = .337, <em>p</em>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Moderate OSA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.04</td>
<td>0.81</td>
<td>1.04</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>-1.15</td>
<td>0.21</td>
<td>0.32</td>
</tr>
<tr>
<td>BMI z Score</td>
<td>0.07</td>
<td>0.90</td>
<td>1.07</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.44</td>
<td>0.04</td>
<td>1.55</td>
</tr>
</tbody>
</table>
## Results: Multinomial Logistic Regression Analysis of the Effect Of Moderate-Severe OSA on Elevations in Fasting Insulin and HOMA-IR Independent of BMI z Score

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<td></td>
<td></td>
</tr>
<tr>
<td>Severe OSA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.11</td>
<td>0.57</td>
<td>0.90</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>-1.92</td>
<td>0.11</td>
<td>0.14</td>
</tr>
<tr>
<td>BMI z Score</td>
<td>0.32</td>
<td>0.57</td>
<td>1.34</td>
</tr>
<tr>
<td><strong>Fasting Insulin</strong></td>
<td><strong>0.16</strong></td>
<td><strong>&lt;0.01</strong></td>
<td><strong>1.20</strong></td>
</tr>
<tr>
<td><strong>Pseudo R² (Snell &amp; Cox) = .337, p&lt;0.001</strong></td>
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</tr>
<tr>
<td>Severe OSA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.13</td>
<td>0.52</td>
<td>0.88</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>-2.20</td>
<td>0.08</td>
<td>0.11</td>
</tr>
<tr>
<td>BMI z Score</td>
<td>0.40</td>
<td>0.48</td>
<td>1.49</td>
</tr>
<tr>
<td><strong>HOMA-IR</strong></td>
<td><strong>0.67</strong></td>
<td><strong>&lt;0.01</strong></td>
<td><strong>1.96</strong></td>
</tr>
</tbody>
</table>
Insulin resistance syndrome

Insulin resistance

 ↑LDL  ↓HDL  ↑TG  ↑BP  ↑Glucose

Interruption Hypoxia

Sleep Fragmentation, Arousals, Sleep Duration,

↑Sympathetic activity

Dyslipidemia

Inflammation

↑Cortisol, ROS

Altered appetite regulation

Increased food intake

↑Leptin  ↑Ghrelin
Metabolic Alterations in OSA: Conclusions

- OSA severity is associated with HOMA-IR even after controlling for the Age, BMI and TST in young children.

- Components of the Metabolic Syndrome known to be associated with an increased risk for cardiovascular disease, including insulin resistance start developing in childhood, and appear to be related to the severity of OSA.
Further studies are required to determine the effect of interventions (like T&A/CPAP/weight reduction/exercise training/dietary changes) on glucose levels and insulin resistance.
Challenge

- Lack of standard definition of OSA and Metabolic syndrome *per se* in pediatric population

Suggested Solution

- We need to conduct an extensive literature survey and propose consensus for OSA
Metabolic Alterations in OSA: References


Acknowledgement

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