Asthma and Obesity in Adults

Symposium 6

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Potential Conflicts of Interest

- Speaker Bureau: AstraZeneca
- Stock: <$20,000 AstraZeneca, ImmunoGen
- Research Paid to University: Forest, Boehringer Ingelheim, Genentech, Merck
- Research Paid to Practice with <$10,000 personal: Genentech
- Legal: Case review < $5,000 not related
- Journal: Allergy Watch, JACI
- Organizations: AMA, ACP, ACCP, AAAAI
Learning Objectives

• To address the question: Does obesity cause asthma or are asthmatic patients more likely to become obese?
• To review how obesity may influence treatment choices in asthma.
Prevalence

Asthma
- Increasing with 6-7% of adults affected
- Increase is greater in developed countries
- Increases dyspnea and exercise intolerance
- Increased burden in select ethnicities (African American and Hispanic in US)

Obesity
- NHANES data in USA shows increase from 15% in 1976-80 to 32.9% in 2003-04
- Increase is greater in developed countries
- Increases dyspnea and exercise intolerance
- Increased burden in select ethnicities and poor
Obesity and Asthma

- One causes or increases the severity of the other, directly or indirectly
  - GERD, sleep apnea
  - Decreased activity, effects of medications
- Coincidental occurrences (shared risk factors)
- Environmental influences increase both simultaneously but through different mechanisms
- One mimics the other (obesity symptoms resemble asthma symptoms)
Asthma and Obesity

Obesity Increases the Incidence of Asthma

- 17 prospective studies, 9 in adults and 8 in children
- Each involved several thousand subjects
- Follow up periods of 2-21 years
- Only 1 failed to show an increased incidence of asthma in the obese
- Obesity antedates asthma
- Many controlled for exercise
- Most show an effect of overweight as well
# Asthma and Obesity

## Obesity and Asthma Control

<table>
<thead>
<tr>
<th>Obesity Reduces Asthma Control</th>
<th>Obesity Doesn’t Reduce Asthma Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dixon et al. (2006)</td>
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<td>Lavoie et al. (2006)</td>
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<td>Peters-Golden et al. (2006)</td>
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<td>Lessard et al. (2008)**</td>
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<td>Mosen et al. (2008)</td>
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<td>Vogt et al. (2008)</td>
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<td>Boulet et al (2007)</td>
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</table>

* Only study performed in children

** Reduced control occurred despite similar ability to perceive symptoms
Asthma and Obesity

Obesity Increases Asthma Severity

- 3095 patients in the National Asthma Survey
- “Compared to non-overweight subjects, obese subjects were significantly more likely to.”

<table>
<thead>
<tr>
<th>Activity</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Report continuous symptoms</td>
<td>1.66</td>
</tr>
<tr>
<td>Miss work</td>
<td>1.35</td>
</tr>
<tr>
<td>Use short acting $\beta_2$ agonists</td>
<td>1.36</td>
</tr>
<tr>
<td>Use inhaled steroids</td>
<td>1.34</td>
</tr>
<tr>
<td>Have severe persistent asthma (GINA class IV)</td>
<td>1.42</td>
</tr>
</tbody>
</table>

Taylor et al.  Thorax, Jan 2008
Associations of Obesity and Asthma

- Ford and Mannino showed with NHANES data 1988-1994 that obese individuals were 44% more likely to have asthma.
- Chen in cross sectional study showed that BMI > 30 associated with asthma OR 2.06 (1.42-4.05) only in females.
- Hancox in adults and children showed that 28% of risk for asthma in females associated with overweight.
Potential Problems in Assessing Relationship

- Difficult to control multiple variables in studies (genetic, environment, behavior)
- Definition of asthma problematic as a syndrome of syndromes (phenotypes of asthma)
- Definition of obesity problematic
  - BMI
  - Total body fat
  - Body fat distribution
  - Type of body fat
Potential Problems in Assessing Relationship

- Asthma medications may be less effective in obese patients
  - Eur Respir J 2006;27:495-503
  - As weight increased, response to inhaled beclomethasone decreased and response to montelukast was not affected
  - Confusion between control and severity
- Weight loss has not consistently improved pathophysiology of asthma (Chest 2000;118:1315-21)
Potential Problems is Assessing Relationship

• Symptoms correlate but diagnosis less clear
  – Dyspnea, cough, wheeze
  – BHR does NOT correlate

• No evidence of association of obesity with atopy, IgE production, eosinophilia

• Severity of asthma may be greater in obesity making association misleading
Potential Mechanisms

• Mechanical effect of weight on breathing physiology
  – Restriction
• Caloric intact modulates asthma
• Adipose cells affect inflammation
  – Proinflammatory adipokine LEPTIN
  – Antiinflammatory adipokine ADIPONECTIN
  – Obesity associated with increases in CRP, TNF, and IL-6
Physiologic Respiratory Factors in Obesity

- Reduced lung volumes (FRC)
- Reduced airway diameter, TV
- Increased airway resistance (males)
- Rapid shallow breathing
- Increased work of breathing
- FEV1/FVC ratio tends to remain normal
  - Decreased compliance due to compression and possible fatty tissue in chest wall
- GERD
Inflammation in Obesity

- Leptin increased, adiponectin decreased
  - Eosinophils with leptin receptors
- TNF, Vascular endothelial growth factor, IL-6, oxidative stress markers increased
- C-reactive protein increased
- TGF-β increased
- Eotaxin increased (studies inconsistent)
- FeNO increased
Animal Models

• Obese mice, both genetic and caloric excess, show increased AHR that correlates with weight and possibly duration of increased weight
  – Lung size inconsistent

• Increased airway response to antigen without Th2 cytokine increase or eosinophils
  – ?role for mast cells and LTAs
Animal Models

- Obese mice have increased response to ozone with BHR, pulmonary resistance and inflammation markers.
- Greater respiratory pathology with respiratory viral infection with obese mice.
- Obese mice have reduced NK cell activity following influenza infection.
Inflammation in Humans

• Decrease in M2 monocytes in adipose tissue with obesity
  – Increase in TNF and IL-6
  – Decrease in inhibitor of IL-1 receptor
  – Monocytes increased with hypoxia of adipose tissue
Hormone Changes

• Leptin increased
  – Satiety hormone and proinflammatory
  – Increased AHR in mice without change in Th2 cytokines or eosinophil influx in airway
  – Increased inflammation response to ozone in mice, possible effect on Toll like receptors
  – Two cross sectional human studies show increase in asthma independent of body mass
    • Could be secondary to airway inflammation
## Associations

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women</th>
<th></th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adiponectin</td>
<td>BMI</td>
<td>Body fat percentage</td>
</tr>
<tr>
<td>Leptin</td>
<td>-0.24</td>
<td>0.76</td>
<td>0.86</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>-0.33</td>
<td>-0.32</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td>0.89</td>
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</table>

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

* All correlations were statistically significant ($P < .001$).
Hormone Changes

• Adiponectin decreased
  – Inverse association with atherosclerosis and type 2 diabetes
  – Augments production of macrophage IL-10 and IL-1 receptor antagonist
  – Suppresses AHR and Th2 cytokines in mice
  – Lung tissue has 3 receptors, one of which (adipoR2), has anti-inflammatory action
    • All 3 reduced following bronchial allergen challenge in mice
    • Decreased FeNO in males
Conclusions

• Both obesity and asthma are increasing in large portions of the world
• Obesity may affect the severity of asthma but is less clear that obesity increases the occurrence of asthma
• Combination of mechanisms likely to link the two conditions
  – Shared comorbidities such as GERD
  – Physical effects
  – Hormonal effects
Challenges

• Not clear that animal models will be sufficient to explain possible relationships
• Cross sectional and epidemiologic studies are unlikely to provide answers but may help generate questions
• Hypothesis driven prospective studies will be needed but are exceedingly difficult due to duration of treatment and difficulties with multiple variables and controls