The Clinical Phenotype of Asthma in Obesity

Anne Dixon, MA, BM, BCh
Outline

• Epidemiology

• How obesity effects clinical phenotype

• Phenotypes of asthma in the obese
Obesity Trends* Among U.S. Adults

(*BMI ≥30, or about 30 lbs. overweight for 5’4” person)
Risk of Adult Onset Asthma

![Graph showing the relationship between Body Mass Index and Relative Risk of Adult Onset Asthma.](image)

Co-morbidities in bariatric surgery

<table>
<thead>
<tr>
<th>Condition</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 2559</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>51.7</td>
</tr>
<tr>
<td>Sleep apnea (%)</td>
<td>41.5</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>31</td>
</tr>
<tr>
<td>Asthma (%)</td>
<td>21.2</td>
</tr>
<tr>
<td>DVT/PE (%)</td>
<td>3</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Asthma in the obese

• Is it really asthma?

• Asthma is usually diagnosed by a combination of history and physiological changes
  – Reversible airflow obstruction
  – Bronchial hyperreactivity
Over-diagnosis of asthma?

71% non-obese confirmed asthma
68% obese confirmed asthma

Aaron SD et al. *CMAJ.* 2008; 179:1121-1131
Overdiagnosis of asthma

• Common in all BMI categories

• Not different in those with a BMI > 30
Does obesity alter the phenotype of asthma?

- Clinical Characteristics
  - control
  - response to treatment

- Atopy and Airway Inflammation

- Airway Physiology

- Phenotypes of asthma in the obese
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patient Population</th>
<th>n</th>
<th>Finding in those with BMI &gt; 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akerman</td>
<td>2004</td>
<td>asthma clinic (US)</td>
<td>143</td>
<td>more severe asthma</td>
</tr>
<tr>
<td>Lavoie</td>
<td>2006</td>
<td>asthma clinic (Canada)</td>
<td>382</td>
<td>worse control and QOL</td>
</tr>
<tr>
<td>Wen</td>
<td>2009</td>
<td>population based (BRFSS) (US)</td>
<td>9668</td>
<td>more likely to report asthma attack in last 12 months</td>
</tr>
<tr>
<td>Dixon</td>
<td>2006</td>
<td>poorly controlled asthmatics</td>
<td>488</td>
<td>no clinically significant differences in lung function or control</td>
</tr>
<tr>
<td>Saint Pierre</td>
<td>2006</td>
<td>4 asthma clinics (France)</td>
<td>406</td>
<td>less likely to achieve asthma control</td>
</tr>
<tr>
<td>Vortmannann</td>
<td>2008</td>
<td>asthmatics recently hospitalized for asthma</td>
<td>843</td>
<td>more symptoms, worse QOL</td>
</tr>
<tr>
<td>Taylor</td>
<td>2008</td>
<td>national asthma survey</td>
<td>3095</td>
<td>increased asthma severity</td>
</tr>
<tr>
<td>Mosen*</td>
<td>2008</td>
<td>managed care organization (US)</td>
<td>1113</td>
<td>worse control, QOL and increased hospitalizations</td>
</tr>
<tr>
<td>Sutherland</td>
<td>2009</td>
<td>mild-to moderate-persistent asthmatics</td>
<td>1265</td>
<td>no clinically significant differences in lung function or control</td>
</tr>
<tr>
<td>Clerimse</td>
<td>2009</td>
<td>Asthmatics from primary care clinics</td>
<td>292</td>
<td>No difference in asthma control</td>
</tr>
</tbody>
</table>

*Obese had 4.6 fold increase risk of hospitalization compared with non-obese
## Surgical weight loss

<table>
<thead>
<tr>
<th>Author</th>
<th>Participants</th>
<th>n</th>
<th>Intervention</th>
<th>Start BMI</th>
<th>End BMI</th>
<th>Improved Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dixon (1999)</td>
<td>&quot;asthmatics&quot;</td>
<td>32</td>
<td>Lap. Band at least 1 year</td>
<td>45.7</td>
<td>32.9</td>
<td>symptomsomedication use</td>
</tr>
<tr>
<td>Dhabuwala (2000)</td>
<td>&quot;asthmatics&quot;</td>
<td>34</td>
<td>silastic ring gastric bypass; median 2.5 years</td>
<td>45</td>
<td>28</td>
<td>medication use</td>
</tr>
<tr>
<td>Narbro (2002)</td>
<td>&quot;asthmatics&quot;</td>
<td>21</td>
<td>surgery vs. conventional Rx</td>
<td>41.8</td>
<td>-16%</td>
<td>non-significant reduction med costs</td>
</tr>
<tr>
<td></td>
<td>&quot;asthmatics&quot;</td>
<td>34</td>
<td></td>
<td>39.9</td>
<td>+1%</td>
<td></td>
</tr>
<tr>
<td>Spivak (2005)</td>
<td>&quot;asthmatics&quot;</td>
<td>11</td>
<td>Lap. band 18 months</td>
<td>45.2</td>
<td>35.1</td>
<td>Resolved in 9 not improved in 2</td>
</tr>
<tr>
<td>Maniscalco (2007)</td>
<td>asthmatics all female</td>
<td>12</td>
<td>Lap. Band (1 year FU)</td>
<td>45.2</td>
<td>34.8</td>
<td>FEV1, FVC symptoms (ACT)</td>
</tr>
</tbody>
</table>
Post Surgical Asthma Control

months post surgery

$p < 0.0001$

Unpublished data
Asthma Control and BMI - Summary

• Obesity tends to be associated with poor asthma control

• Significant weight loss is associated with improvements in asthma control
Response to Treatment in Obese Asthmatics
Effect of Theophylline on Exacerbations in Obese

Dixon 2006, J Asthma
Response to Controller Therapy

- Peters Golden ERJ 2006

![Graph showing response to controller therapy for different conditions.](image)

- Normal
- Overweight
- Obese

% Asthma Control Days

Montelukast
Beclomethasone
Placebo

Boulet, Respir Med. 2007
Sutherland, JACI 2009
Camargo J Asthma, 2010
Glucocorticoid sensitivity altered in PBMC of obese asthmatics

Asthma

Sutherland ER AJRCCM. 2008
Response to therapy - Summary

- Altered in obese asthmatics
- May in part be related to reduced glucocorticoid responsiveness

*Important consideration in design of future asthma treatment trials and patient care*
Obesity and allergic airway inflammation
Risk of asthma in relation to atopy

Atopic women

Non-atopic women

Chen 2006, CHEST
Jarvis, 2002
Kronander 2004
Chen 2009
Airway inflammation in obese asthmatics

van Veen Allergy 2008
Effect of weight loss on airway inflammation
BAL Eotaxin in asthmatics pre and post weight loss surgery

A box plot showing Eotaxin levels before operation (Pre Op) and 12 months post-operation. The plot indicates a significant decrease in Eotaxin levels post-operation compared to pre-operation, with a p-value of P < 0.01. The unpublished data suggests a positive outcome for weight loss surgery in managing asthma.

Unpublished data
Effect of weight loss on cytokine production from peripheral blood CD4 cells

CD4 cells isolated from peripheral blood and stimulated by CD3/CD28 before (0) and 12 months after (12) weight loss surgery

Unpublished data
Allergic airway inflammation in the obese - summary

- Inverse relationship between airway eosinophilia and BMI
- Reduced FeNO in obesity
- Increased eotaxin in BAL with weight loss
- Increased cytokine production by peripheral CD4 cells following weight loss
Obesity is not associated with increased allergic airway inflammation

Obesity may dampen allergic airway inflammation
Effect of Obesity on Airway Function
# Change in Lung Function

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-op</th>
<th>12 mths post</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1*</td>
<td>82.7 ±12.7</td>
<td>94.3 ± 13.0</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>FVC*</td>
<td>85.3 ± 14.2</td>
<td>99.3 ± 16.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FEV/FVC</td>
<td>0.79 ± 0.06</td>
<td>0.77 ± 0.05</td>
<td>0.41</td>
</tr>
<tr>
<td>RV</td>
<td>92.4±20.4</td>
<td>86.6±38.2</td>
<td>0.71</td>
</tr>
<tr>
<td>TLC</td>
<td>87.9±12.8</td>
<td>91.3±18.4</td>
<td>0.68</td>
</tr>
<tr>
<td>FRC</td>
<td>60.7±14.4</td>
<td>80.8±35.8</td>
<td>0.25</td>
</tr>
<tr>
<td>DLCO</td>
<td>95.1±18.4</td>
<td>93.2±10.8</td>
<td>0.89</td>
</tr>
</tbody>
</table>

*percent predicted
Change in impedance with weight loss

Dixon, unpublished
Change in Impedance with weight loss

• Before weight loss surgery
  – Suggests inhomogeneity/increased tissue resistance
  – Stiffer lung/decreased lung units (closure)

• 12 months after weight loss surgery
  – Improvements suggest changes in the periphery consistent with alterations in lung volume and airway closure
Obesity and Lung Mechanics

- At baseline obesity is associated with abnormalities in the periphery of the lung
- Abnormal compliance of the lung in obesity
  - Microatelectasis
  - Surfactant function
  - Blood volume
Effect of obesity on airway hyperresponsiveness
Obese breathe at low lung volumes
Breathing at low lung volumes can lead to airway hyperreactivity
Obese have Dynamic Hyperinflation in response to Methacholine challenge

<table>
<thead>
<tr>
<th></th>
<th>obese</th>
<th>normal</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>fall in FEV1*</td>
<td>23 ± 8</td>
<td>23 ± 9</td>
<td>0.71</td>
</tr>
<tr>
<td>fall in FVC*</td>
<td>18 ± 8</td>
<td>13 ± 6</td>
<td>0.002</td>
</tr>
<tr>
<td>fall in IC *</td>
<td>26 ± 14</td>
<td>15 ± 12</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>increase in FRC *</td>
<td>20 ± 17</td>
<td>13 ± 12</td>
<td>0.007</td>
</tr>
</tbody>
</table>

| increase in reactance †| 2.82 ± 1.72 | 1.50 ± 1.60 | 0.008  |

*asthmatics, values expressed as % predicted
†non-asthmatics, value expressed as cmH₂O 1·s⁻¹

*Deesomchok, AJRCCM, 2010
†Salome, Int J Obesity, 2007

Sutherland, AJRCCM, 2008
Effect of Weight loss on AHR

Unpublished data
Change in AHR by atopic status

Non-atopic, $p=0.04$
Atopic, $p = 0.75$

Unpublished data
AHR and Obesity - Summary

• Obesity may lead to a distinct form of AHR characterized by *dynamic hyperinflation* and *decreased peripheral lung compliance*

• AHR tends to improve in those with non-atopic asthma

• (obesity may dampen allergic inflammation)
Two Phenotypes of Asthma in the Obese

- Early onset atopic asthma, that happen to be obese
- Non-atopic with late onset asthma that develops in the setting of obesity
Speculation

Obesity

Airway Hyperresponsiveness

"Asthma" in the Obese Patient

Allergic airway inflammation and remodeling
Take Home

• Obesity is a risk factor for the development of asthma

• Obese have poorly controlled asthma
  – Does not respond as well to treatment

• Obesity *does not* increase allergic airway inflammation

• Obese have distinct form of AHR
  – AHR improves only in those with non-allergic asthma