Asthma and obesity, implications for airway inflammation and Bronchial Hyperresponsiveness

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Mapa 1.4
Distribución de la prevalencia de sobrepeso y obesidad en población escolar (5 a 11 años) por entidad federativa, ENSANUT 2006

2006

Prevalencia de sobrepeso y obesidad
- >= 30 Muy alta
- >= 20 y < 30 Alta
- >= 15 y < 20 Moderada
- < 15 Baja
Obesity Trends* Among U.S. Adults
(*BMI ≥30, or about 30 lbs. overweight for 5’4” person)
How can obesity lead to BHR?

- Increased chest wall restriction
- Increased airway resistance
- Lower tidal volumes (reduced tidal length perturbations in the AMS)
- Reduced tidal-length perturbation
- ASM in static equilibrium
- ASM in a “latch or frozen state”

Proposed scheme for the mechanical effects of obesity on airway function

A. Tidal breathing
   Large cyclic strains on ASM
   ASM cells compliant
   ASM cells long, airway caliber large

B. Obesity
   ↓FRC
   ↓Peribronchial pressure
   ↓Tidal Breathing
   Small cyclic strains on ASM
   ASM cells stiff

Bronchial hyperreactivity

Dynamic state
Rapid cycling
actin –myosin bridges

Frozen state or
Latch state

Shore et al, Pharm Ther 2006;103:86-102
Airway resistance and BMI

Adults with asthma

n=140 (102 asthmatics)

Median Raw in asthmatics

Healthy controls

Holguin et al, 2010
Paradoxically, obese asthmatics bronchoconstrict, instead of bronchodilating, after a deep breath.

Holguin et al, 2010
Increasing airway hyperresponsiveness as a function of BMI

41 healthy non-smoking adults

Torchio et al, 2009
Increasing BMI and the odds of BHR

From the Nornative Aging Study
61 cases & 244 matched controls


<table>
<thead>
<tr>
<th>Quintiles of baseline BMI (kg/m²)</th>
<th>No (%) of cases</th>
<th>Univariate OR (95% CI)</th>
<th>Multivariable* OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤24.3</td>
<td>16 (26.2%)</td>
<td>7.0 (1.8 to 27.7)</td>
<td>7.5 (1.3 to 44.7)</td>
</tr>
<tr>
<td>&gt;24.3–25.9</td>
<td>11 (18.0%)</td>
<td>3.9 (1.0 to 15.0)</td>
<td>4.1 (0.7 to 25.0)</td>
</tr>
<tr>
<td>&gt;25.9–27.3</td>
<td>3 (5.9%)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt;27.3–29.4</td>
<td>11 (18.0%)</td>
<td>4.2 (1.0 to 16.9)</td>
<td>3.6 (0.7 to 18.5)</td>
</tr>
<tr>
<td>&gt;29.4</td>
<td>20 (32.8%)</td>
<td>10.0 (2.6 to 37.9)</td>
<td>7.5 (1.5 to 37.8)</td>
</tr>
</tbody>
</table>

*Model adjusted for age, smoking status (current, former, and never smoker), pack years of smoking, log_{10} IgE, and initial FEV₁.
Relation between body mass index (kg/m2) and risk of asthma and symptomatic airway hyperresponsiveness in 3,386 men in Anqing, adjusting for age, intensity of cigarette smoking, skin test reactivity to one or more allergens, and familial correlations.
Relation between body mass index (kg/m2) and risk of asthma and symptomatic airway hyperresponsiveness in 3,723 women in Anqing, adjusting for age, intensity of cigarette smoking, skin test reactivity to one or more allergens, and familial correlations.

Celedon JC et al 2001
# Does obesity increase BHR?

## Table 1. Studies on the Relationship between AHR and BMI

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>n</th>
<th>Approx. Age</th>
<th>Type of Study</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang, 1999</td>
<td>Taiwan</td>
<td>1,459</td>
<td>“Junior High”</td>
<td>Cross-sectional</td>
<td>Relationship between AHR and BMI, girls only</td>
</tr>
<tr>
<td>Celedon, 2001</td>
<td>China</td>
<td>7,109</td>
<td>Mean = 37</td>
<td>Cross-sectional</td>
<td>Relationship between symptomatic AHR and BMI</td>
</tr>
<tr>
<td>Schachter, 2001</td>
<td>Australia</td>
<td>1,971</td>
<td>Mean = 35</td>
<td>Cross-sectional, pooled</td>
<td>No relationship AHR and BMI</td>
</tr>
<tr>
<td>Chinn, 2002</td>
<td>Europe, Australia, New Zealand, United States</td>
<td>11,277</td>
<td>20–44</td>
<td>Cross-sectional</td>
<td>Relationship between AHR and BMI, significant in men only</td>
</tr>
<tr>
<td>Litonjua, 2002</td>
<td>United States</td>
<td>61 with new-onset AHR and 244 matched control subjects</td>
<td>Mean = 62</td>
<td>Case control</td>
<td>New-onset AHR related to BMI</td>
</tr>
<tr>
<td>Schachter, 2003</td>
<td>Australia</td>
<td>5,933</td>
<td>7–12</td>
<td>Cross-sectional, pooled</td>
<td>No relationship AHR and BMI</td>
</tr>
<tr>
<td>Bustos, 2005</td>
<td>Chile</td>
<td>1,232</td>
<td>early</td>
<td>Cross-sectional</td>
<td>No relationship AHR and BMI</td>
</tr>
<tr>
<td>Hancox, 2005</td>
<td>New Zealand</td>
<td>~ 1,000</td>
<td>9–26</td>
<td>Cross-sectional</td>
<td>No relationship AHR and BMI</td>
</tr>
<tr>
<td>Sood, 2006</td>
<td>United States</td>
<td>1,725</td>
<td>Adults</td>
<td>Cross-sectional, clinic referral population</td>
<td>Relationship between AHR and BMI, only subjects without asthma</td>
</tr>
</tbody>
</table>

Definition of abbreviations: AHR, airway hyperresponsiveness; BMI, body mass index.

Raviv et al, cross sectional study of 226 participants from 2 ALA-ACRC studies, found no association between BMI and BHR, after stratifying by the degree of airway obstruction

Raviv et al *J Asthma*, pending; Dixon, A et al, *PATS* 2010
Obesity and BHR, one size doesn't fit all

Enrolled asthmatic participants
n = 41

- 9 no response to methacholine/bronchodilator
- 1 started prohibited medication
- 6 no bariatric surgery
- 2 withdrew from study

Asthmatic participants undergoing bariatric surgery and bronchoscopy
n = 23

- 2 lost to follow up

Follow up at 12 months
n = 21

Enrolled non-asthmatics
n = 35

- 9 responded to methacholine
- 3 withdrew from study

non-asthmatic participants undergoing bariatric surgery and bronchoscopy
n = 21
Weight-loss mediated reductions in BHR, by IgE levels
Obesity and airway inflammation

No evidence that obesity leads to increased biomarkers of airway inflammation

Beuther, et al 2007
### Association between BMI and sputum counts

<table>
<thead>
<tr>
<th></th>
<th>BMI &lt;20 (n=8)</th>
<th>20–24.9 (n=37)</th>
<th>25–29.9 (n=54)</th>
<th>30–30.9 (n=51)</th>
<th>40 (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TCC:</strong></td>
<td>3.2 (0.8–49.5)</td>
<td>2.5 (0.9–28.0)</td>
<td>5.5 (0.3–277.5)</td>
<td>4.4 (0.2–68.8)</td>
<td>5.1 (1.0–37.6)</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>50.6 (28.7)</td>
<td>52.4 (29.7)</td>
<td>57.9 (29.4)</td>
<td>59.2 (27.1)</td>
<td>65.4 (28.8)</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0.4 (0–53.0)</td>
<td>0.7 (0–35.3)</td>
<td>0.4 (0–89.0)</td>
<td>0.7 (0–34.3)</td>
<td>0.3 (0–3.3)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>0.3 (0–2.7)</td>
<td>0.3 (0–5.0)</td>
<td>0.7 (0–4.3)</td>
<td>0.3 (0–4.0)</td>
<td>0.3 (0–1.7)</td>
</tr>
<tr>
<td>Macrophages</td>
<td>36.6 (23.1)</td>
<td>42.8 (28.4)</td>
<td>34.0 (25.9)</td>
<td>36.0 (25.2)</td>
<td>31.8 (28.7)</td>
</tr>
</tbody>
</table>

Todd, et al., Clin & Exp Aergy, 2007
Association between eNO and log-Eosinophils

136 asthmatics with difficult to treat asthma

I.H. Van Veen, Allergy 2008
Association between exhaled NO (log) and BMI in asthmatics Participating in the Severe Asthma Research Program (SARP)

N=799

Body mass index, kg/m^2

BMI <30
BMI ≥ 30

95% CI
Linear fit

p < 0.01

N=799
Decreased Fraction of Exhaled Nitric Oxide in Obese Subjects With Asthma Symptoms

2,187 Sweden cohort
Among those with wheezing (19%), FeNO was negatively related to BMI, waist to hip ratio and % body fat.

Atopy % similar in wheezing and no wheezing groups

Berg et al, 2011
Obesity and overweight, not associated with lower FeNO in children

School-based 800 children (ages 10 – 16)  Cibella, 2011
Obesity and asthma, an interaction on *neutrophilic* but not *eosinophilic* airway inflammation.

Adult asthmatics (115/197) with evidence of AHR, of which > 50% had moderate to severe asthma.

Two-way factorial interaction for obesity and asthma on airway neutrophilia, p=0.01.

Scott, et al 2011
Is it possible that in childhood – onset asthmatics, weight gain generally occurs as a consequence of the underlying disease severity?

And that in adult onset asthmatics (specially among those with less eosinophilic/atopic asthma), obesity may be a risk factor for the development of asthma?
Age of asthma onset, and change in BMI

FIG 1. Association between BMI and years of having asthma by age of asthma onset. Linear regression models are adjusted for sex, race, and asthma severity. Early-onset asthma linear slope: $\beta = 0.20$; 95% CI, 0.07 to 0.33; $P = .002$. Late-onset asthma slope: $\beta = -0.05$; 95% CI, $-0.17$ to 0.33; $P = .4$. Interaction of BMI and asthma duration by age of onset of asthma: $P < .008$.  

Holguin, et al 2011
The obese asthma phenotype

Late asthma onset
Moore (>23)
Haldat (35)

Lower atopy %

Highly symptomatic
Symptoms out of proportion to
The degree of airway obstruction or
airway eosinophilia

Higher female Proportion,
Older
Exhaled NO and BMI, an association modified by age of asthma onset

Linear regression of log-eNO and BMI

SARP, based on 799 adults
BHR in obese asthmatics, by age of asthma onset

SARP participants

p=0.009
Although both systemic and airway inflammation were demonstrated with obesity and asthma, there was no clear evidence of an interaction between the two.

JT Sutherland, 2008
Asthma

Exacerbations

FEV1

Phenotype A

Phenotype B

Phenotype C

Phenotype D

Symptoms

Th2 inflammation

No/less Th2 inflammation

Early Onset

Late Onset

Table:

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Age onset physiology</th>
<th>Clinical</th>
<th>Biomarkers</th>
<th>Genetics</th>
<th>Response to Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity Phenotype</td>
<td>Adult onset Severity not explained by obstruction/airway eosinophils</td>
<td>Women, very symptomatic Airway hyper-responsiveness less clear</td>
<td>Lack of Th2 biomarkers</td>
<td>Weight loss, hormonal?</td>
<td></td>
</tr>
</tbody>
</table>

Sally Wenzel 2011
Obesity and asthma, what are the implications for AHR and airway inflammation?

• Increasing BMI has been associated with BHR by mechanisms that are not well defined
• There does not appear to be an interaction between obesity and asthma on BHR
• Obesity is not associated with increased Th2-type airway biomarkers of inflammation
• Obesity – related changes in airway inflammation may depend on other phenotypical characteristics (age of asthma onset)