Obstructive Sleep Apnea and Obstructive Airway Diseases

Interactions
Conflicts of Interest

Work:
Funded by University of Alberta

Research:
GSK, AZ, BI; Public Health Agency of Canada; CADTH

Honoraria:
Bayer, NycoMed, Novartis, GSK, AZ, BI

Speaker Fees:
Vitalaire, NycoMed, Taketa, BI
Objectives

• 1. Review the prevalence of OSA and asthma
• 2. Review possible mechanisms of interaction
  – Inflammation
  – Obesity
  – GERD
• 3. Examine future directions
Case

- Ms. JD is a 38 year old woman
- Three ED visits in last 6 months
- Admitted to hospital with asthma exacerbation
  - Three weeks worsening symptoms
    - Waking with dyspnea 3-4 times per night
  - Peak flow 300 L/min
    - Best values of 410 L/min
    - Normally 350-380 L/min
- History of asthma started age 25
  - Evidence of atopy, IgE minimally elevated, no eosinophils seen while receiving prednisone, treated hypertension
Case

• Treated with prednisone, bronchodilators
  – In hospital slow improvement
  – Diffuse wheeze improved
• Noted to have BMI = 38
  – Gained 15 kg over 5 years
    • Aggravated by multiple courses of prednisone
  – Mild daytime somnolence
  – Snore keeping room-mate awake
Kananaskis, Alberta
Sleep and Asthma

• Nocturnal asthma can cause sleep disruption
  – Nocturnal exacerbations affect about 2/3 asthma patients
  – Signal of poor control
  – Can result in excessive daytime somnolence

• How much of the sleepiness is related to comorbid OSA
Asthma and Sleepiness

- Consecutive patients (n=156) undergoing routine asthma care
  - 47% excessive daytime somnolence by questionnaire (ESS)
    - General population 9% to 15% excessive sleepiness
  - High likelihood OSA by questionnaire in 39 (49%) of the women and 12 (33%) of the men
- Majority of sleepiness due to comorbid, undiagnosed OSA

Teodorescu et al., Sleep Medicine 7:2006; 607–613
Sleep, Asthma and OSA

- OSA may cause nocturnal awakenings
  - Arousal from apneas/hypopneas confused with asthma
- Snoring may trigger neural reflexes causing bronchoconstriction
  - e.g. increased vagal tone secondary apneas/hypopneas
- OSA may worsen nocturnal GERD
- OSA may worsen nocturnal asthma
  - Hypoxia-induced increased bronchial responsiveness
- Rhinitis associated with asthma/allergy may worsen OSA
- Reduced airway cross-sectional area may worsen OSA
  - Increased airway mucosal inflammation in asthma
Canmore, Alberta
EVERYTHING INTERCONNECTED.
WHAT CAME FIRST- ASTHMA OR OSA?
CHICKENS OR EGGS?
WHAT IS DESCRIPTION OF TYPICAL SLEEP APNEA PATIENT?
OSA Patient Characteristics
STOP-Bang Score

• **Snoring**
  – Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?

• **Tired**
  – Do you often feel *tired, fatigued, or sleepy during daytime*?

• **Observed apnea**
  – Has anyone observed you stop breathing during your sleep?

• **Blood pressure**
  – Do you have or are you being treated for high blood pressure?

Cheung et al., Anesthesiology 2008; 108:812–21
OSA Characteristics
STOP-Bang Score

• **BMI**
  – BMI more than 35 kg/m²?

• **Age**
  – Age over 50 yr old?

• **Neck circumference**
  – Neck circumference greater than 40 cm?

• **Gender**
  – Gender male?

• **High risk of OSA**: answering yes to three or more items
  – 84% sensitivity for moderate OSA

• **Low risk of OSA**: answering yes to less than three items
  – 61% negative prediction for moderate OSA

Cheung et al. Anesthesiology 2008; 108:812–21
ASTHMA IS A COMMON ADULT CHRONIC ILLNESS IN CANADA
**Asthma Prevalence in Canada**

- The prevalence of physician diagnosed asthma among Canadians 12 years of age and over is 8.3% overall (2.2 million Canadians)
- In 2005, 70.8% of individuals (+12 years of age) with asthma had asthma symptoms or an attack or used medications for asthma in the previous 12 months

<table>
<thead>
<tr>
<th>AGE GROUP (YEARS)</th>
<th>MEN</th>
<th>WOMEN</th>
<th>TOTAL</th>
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<tbody>
<tr>
<td></td>
<td>%</td>
<td>Number</td>
<td>%</td>
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<tr>
<td>12-19</td>
<td>11.9</td>
<td>203,800</td>
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<td>20-44</td>
<td>6.9</td>
<td>396,500</td>
<td>10.1</td>
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<td>45-64</td>
<td>5.1</td>
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<td>9.2</td>
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<tr>
<td>65+</td>
<td>6.8</td>
<td>117,900</td>
<td>8.1</td>
</tr>
</tbody>
</table>

AND OBSTRUCTIVE SLEEP APNEA IS ALSO COMMON
Typical OSA Patient

- Typical patient
  - Male, middle-aged, overweight
- Typical co-morbidity
  - Hypertension
- Typical clinical complaint
  - Sleepy, snoring, witnessed apneas
- Very common disorder
  - 4% men and 2% women is the minimum prevalence
    - Note best survey is almost 20 years old
  - Atypical presentations are still often found
    - Young, thin women can also have OSA

More Contemporary Prevalence Data

• Young et al population survey assessed working age population using Level 1 PSG
  – This study has best quality data but published 1993

• National Sleep Foundation (USA) polled 1,506 adults in 2005
  – Berlin Questionnaire is a validated tool for OSA
  – 26% met high probability criteria of having OSA

Hiestand et al., CHEST 2006; 130:780–786
Where are population trends going

USA Population BMI >40

USA Population BMI >30

Almost 40% of USA population will have BMI >30 by 2023

Almost 10% of USA population will have BMI >40 by 2023
Patients at Risk of OSA

Distribution of high risk OSA by age and gender US population (2006)

Distribution of high risk OSA by BMI US population (2006)

Hiestand et al., CHEST 2006; 130:780–786
Emerald Lake, British Columbia
ROLE OF OBESITY IN ASTHMA
EFFECTS OF WEIGHT REDUCTION
Link Obesity to Asthma

- Canadian population survey showed increased risk of asthma with increased BMI in women$^1$
  - BMI >30 kg/m$^2$ versus BMI =20 -24.9 kg/m$^2$
    - OR 1.9 women (significant)
    - OR 1.1 men (not significant)

- More recent American survey in black women showed similar risks$^2$
  - Compared to BMI of 20 to 24
    - Multivariate incidence rate ratio (IRR) increased from 1.26 for BMI= 25-29 to 2.85 for BMI> 40; P < 0.0001;

2. Coogan et al., J Allergy Clin Immunol 2009;123:89-95
Asthma and Obesity are Linked

- Recent workshop summarized effects of obesity on asthma
- Leptin increased and adiponectin decreased in obesity
  - Leptin pro-inflammatory
  - Adiponectin anti-inflammatory

IS DIFFICULT TO TREAT ASTHMA INFLUENCED BY OBESITY?
Difficult to Treat Asthma

- Difficult to treat asthma (n=136) were examined
  - BMI ≥30 (n= 29)
  - BMI <30 (n= 107)
- hs-CRP (mg/l) higher in obese
  - Non-Obese CRP= 2.5 (0.5–65.3)
  - Obese CRP= 8.1 (0.5–33.7)
  - p< 0.003
- More OSA and GERD in obese

Van Teen et al., Allergy 2008: 63: 570–574
Obesity and Difficult to Treat Asthma: Less Eosinophilic Inflammation

Higher BMI, lower eosinophils

Higher BMI, lower FeNO

Less inflammation in obese suggest that they have milder asthma and if lost weight might actually be much easier to control. Focus on GERD and weight loss for therapy.

Van Teen et al., Allergy 2008: 63: 570–574
ETIOLOGIC LINK MAY BE THROUGH ALTERED INFLAMMATION
Airway Neutrophils Increased in OSA and Obesity

- There were increased neutrophils in induced sputum in obese
  - These subjects did not have asthma
- Non-significant trend for obese-OSA to have highest neutrophil counts

Carpagnano et al., Translational Res 2010;155:35–43
Airway Inflammation and Obesity

Sputum Eosinophils
Horizontal bar = median

Sputum Neutrophils
Horizontal bar = mean

Increased eosinophils in asthma vs non-asthma

Scott et al., Eur Respir J 2011; 38: 594–602
**Airway Inflammation and Obesity**

- Obese asthmatic increased sputum neutrophils but not eosinophils
  - Neutrophilic asthma defined as \( \geq 61\% \) neutrophils
- Sputum neutrophils positively correlated with BMI in women but not men
  - 1% increase in neutrophils for every 1 unit increase BMI in women

Scott et al., Eur Respir J 2011; 38: 594–602
Obesity and Asthma Phenotype

- Cluster analysis shows a phenotype of obese, predominately female, without airway eosinophils

Leptin and Adiponectin

• Levels of leptin and adiponectin similar between obese asthmatic (n=22) and obese non-asthmatics (n=20)
  – Increased leptin and decreased adiponectin found in obesity
    • Tends to skew toward Th1 response

• Hypothesize that obesity skew toward Th1 helps create the obese asthma phenotype

Golden, British Columbia
IF OBESITY INCREASES RISK OF ASTHMA WHAT ARE THE EFFECTS OF WEIGHT REDUCTION?
Effect of Bariatric Surgery in Morbidly Obese Asthmatics

- Twenty-three patients with asthma prospectively studied
  - Twelve subjects (intervention) to undergo bariatric surgery
    - BMI range 39-60 kg/m²
  - Eleven subjects (control) on wait list for surgery
    - BMI range 35-69 kg/m²
  - One year follow post-op bariatric surgery
    - Control group also followed for one year from enrolment

Effects of Bariatric Surgery

• Intervention group showed multiple improvements
  – BMI decreased from 51.2±7.3 kg/m² to 34.4±4.3 kg/m² at 12 months
  – PC₂₀ methacholine improved by a mean 2.7 doubling concentrations at 12 months (P < 0.001)
    • 0.84 mg/ml pre-op to 6.24 mg/ml 12 month post-op
  – FEV₁ percent predicted improved from 95±15 to 106±10 (p<0.001)
  – hs-CRP improved from 8.6±6.3 to 1.7±2.2 mg/L at 12 months (P < 0.001)
• Control group BMI, PC₂₀, hs-CRP and FEV₁ did not change over 12 months of observation

Summary

• Asthma and obesity are linked
• Obesity associated with harder to control asthma
• Obesity increases airway neutrophilic inflammation
• Obesity skews toward Th1 type response
• Treating obesity improves asthma control and systemic inflammation
Emerald Lake, British Columbia
OSA AND ASTHMA
Difficult to Treat Asthma and OSA

• Patients were recruited from Difficult to Treat asthma program
  – Total 78 subjects equally distributed between Severe, Moderate and Control groups
  – Subjects underwent home study that included EEG, EOG and EMG in addition to respiratory variables

Julien et al., J Allergy Clin Immunol 2009;124:371-6
Subject Characteristics

- Increase AHI in Severe vs Moderate vs Control
  - Total AHI >15 events/h
    - Severe 23/26 (88%)
    - Moderate 15/26 (58%)
    - Control 8/26 (31%)
- In severe asthma should consider and/or evaluate for concurrent OSA

Julien et al., J Allergy Clin Immunol 2009;124:371-6
Uncontrolled Asthma and OSA

• Population drawn from asthma clinic (n=472)
  – High risk OSA by validated questionnaire
  – Asthma control by ACQ $\geq 1.5$

• After correcting for obesity, presence of GERD, nasal disease OSA was still significant
  – Uncontrolled asthma OR = 3.01 for having OSA

• Patients difficult to control asthma should be screened for OSA

Teodorescu et al., CHEST 2010; 138:543–550
Asthma Control, Obesity and Inflammation

BMI not related to ACQ during baseline conditions

After 3 months high dose ICS then BMI was related to ACQ

Farah, et al., CHEST 2011; 140:659–666
Summary

• There is a linkage between difficult to treat asthma and sleep apnea
  – This is seen even when controlled for obesity

• There is a relationship of worsening asthma control with increasing BMI
  – This is seen after ICS responsive inflammation is treated

• In patients with OSA factors that result in difficult to treat asthma are not well understood
COPD AND OSA INTERACTIONS
OSA and COPD

• Overlap syndrome is common
  – Both COPD and OSA common conditions

• OSA with COPD compared to OSA without COPD
  – More frequent episodes of oxygen desaturation
  – More total sleep time with hypoxemia
  – More severe hypercapnia
  – More likely to develop daytime pulmonary hypertension
  – More likely to develop right heart failure

Cohort Study

- Patients with COPD without OSA (apnea-hypopnea index > AHI, 5 events/hour sleep)
  - N=210
- Patients with COPD and OSA (overlap syndrome) not treated with CPAP
  - N=213
- Patients with overlap syndrome treated with CPAP
  - N=228

Marin et al., Am J Respir Crit Care Med 182:325–331, 2010
Baseline Characteristics

- The three cohorts were similar in terms of COPD
  - FEV$_1$, GOLD stage distribution, inhaler therapy, SaO$_2$
- The Overlap groups had higher BMI
  - Higher AHI, higher ESS, higher prevalence hypertension

Marin et al., Am J Respir Crit Care Med 182:325–331, 2010
Outcomes

Increased Exacerbation Frequency

Increased all Cause Mortality

Marin et al., Am J Respir Crit Care Med 182:325–331, 2010
Mortality

- Untreated overlap greatest mortality
  - Median 9.4 year follow up
  - CVS significantly increased
  - All cause significantly increased
  - Pulmonary trend for increase

Marin et al., Am J Respir Crit Care Med 182:325–331, 2010
COPD with Daytime Hypoxia

• A group of patients receiving long term oxygen therapy (LTOT)
  – 61 with OSA elected to use CPAP
  – 34 with OSA elected to not use CPAP

• Numbers relatively small and patients self-selected

Key Messages

• Search for OSA in patients with asthma
• Majority of patients with difficult to treat asthma have associated OSA
• Treat morbid obesity to improve OSA as well as improve asthma control
• Overlap syndrome (OSA and COPD) increased mortality
  – CPAP treatment reduces mortality
EXTRA SLIDES
Effects of Albuterol During Acute Asthma in Emergency Room

Obese presented with slightly higher PEFR than non-obese

The acute response to treatment was similar across all severity

Airflow Obstruction and OSA

- Sixty-seven subjects with asthma or COPD
  - Tertiary referral to Pulmonary Outpatient clinic
  - 38/29 had COPD/asthma
- Control group were relatives without known asthma or COPD
- Screened with Berlin Questionnaire
  - 55%, 62.1% and 7.5% of COPD, asthma and control at high risk for OSA
  - High probability for OSA referred Level 1 PSG
    - 24/26 high probability had OSA confirmed
- BMI only factor with significant association with OSA risk
  - No association of OSA risk with FEV$_1$

Sharma et al., Lung 189:37–41, 2011