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Effects of Obstructive Sleep Apnea and Gastroesophageal Reflux Disease on Asthma Control in Obesity

Anne E. Dixon, MD¹, Emmanuelle M. Clerisme-Beaty, MD, MHS², Elizabeth A. Sugar, PhD², Rubin I. Cohen, MD³, Jason E. Lang, MD⁴, Ellen D. Brown, MS², Joel E. Richter, MD⁵, Charles G. Irvin, PhD¹, and John G. Mastronarde, MD⁶ for the American Lung Association-AsthmaClinical Research Centers^{*}

¹University of Vermont

²Johns Hopkins University

³North Shore-Long Island Jewish Health System

⁴Nemours Children's Clinic

⁵Temple University

⁶The Ohio State

Abstract

Background—Obesity is a risk factor for asthma. Obese asthmatics often have poor asthma control and respond poorly to therapy. It has been suggested that co-morbidities associated with obesity, such as reflux and obstructive sleep apnea, could be important factors contributing to poor asthma control in obese patients.

Objectives—The purpose of this study was to determine if (i) reflux and/or (ii) symptoms of sleep apnea contribute to poor asthma control in obesity.

Methods—We studied asthmatic subjects participating in a trial of reflux treatment. Participants underwent baseline evaluation of asthma symptoms and lung function. 304 participants underwent esophageal pH probe testing. 246 participants were evaluated for obstructive sleep apnea symptoms.

Results—Of 402 participants in this trial, 51% were obese.

Role of reflux in asthma control: Those with higher body mass index reported a higher prevalence of reflux symptoms, but the prevalence of pH probe acid reflux was similar in all groups. Reflux was not associated with measures of asthma control in obese patients.

Role of obstructive sleep apnea in asthma control: Symptoms and self-report of obstructive sleep apnea were more common with increasing body mass index and associated with worse asthma control as measured by the Juniper Asthma Control Questionnaire and Asthma Symptom Utility Index.

Conclusions—Our data suggest that obstructive sleep apnea, but not gastroesophageal reflux disease may contribute significantly to poor asthma control in obese patients.

Corresponding Author: Anne E. Dixon, MD, Department of Medicine, University of Vermont College of Medicine, Given 209, 89 Beaumont Avenue, Burlington, VT 05405, anne.dixon@vtmednet.org, Phone: 802 656 8812, Fax: 802 656 3526.

^{*}A complete listing of the American Lung Association Asthma Clinical Research Centers can be found at the end of this article.

Declaration of Interest:

The authors report no other competing interests. The authors alone are responsible for the content and writing of this paper.

Keywords

Obesity; Asthma; lung function; reflux; obstructive sleep apnea

Introduction

Obesity is a risk factor for asthma. With the growing number of overweight and obese individuals world-wide this represents a significant public health problem, particularly because obese asthmatics tend to have poor asthma control and do not respond as well to conventional therapy.^{1,2}

One of the barriers to identifying effective treatments for asthma in the obese is the poor understanding of the pathogenesis of asthma in relationship to obesity. Many have speculated that co-morbidities related to obesity, such as gastro-esophageal reflux disease (GERD) and obstructive sleep apnea (OSA) could lead to respiratory disease in obese individuals.³ Reflux could worsen asthma disease activity through microaspiration of acid into the airway, or vagally-mediated bronchoconstriction.^{4,5} The exact mechanisms linking lower airway disease and OSA are not known, though small studies suggest treatment of sleep apnea may lead to improvements in asthma; given the high prevalence of sleep apnea in obesity, sleep apnea could cause poor asthma control in obese individuals.^{6,7}

The primary purpose of this investigation was to determine if acid reflux and/or OSA are increased in obese asthmatics, and if these co-morbidities are associated with more severe asthma. We hypothesized that these factors would be more prevalent in obese than lean asthmatics, and associated with worse asthma control in the obese. We performed this study in a cohort of patients enrolled in a trial of acid reflux treatment in asthmatics performed by the American Lung Association-Asthma Clinical Research Centers.⁸

Methods

Details of the main study design have been published elsewhere.⁹ Non-smoking individuals with inadequately controlled asthma despite the use of moderate or higher doses of inhaled corticosteroids were enrolled at 19 clinical centers. Inclusion criteria included the following: age 18 years or older; physician-diagnosis of asthma and either a positive methacholine challenge test (for subjects with FEV1 > 70% predicted) or a 12% increase in FEV1 with bronchodilators; 8 weeks of stable use of an inhaled corticosteroid equivalent to 400 ug/day or greater of fluticasone; and poor asthma control defined by Juniper Asthma Control Questionnaire¹⁰ score of 1.5 or greater or more than one acute episode of asthma requiring unscheduled medical care in the past year. Exclusion criteria included the following: smoking in the last 6 months; greater than 10 pack year smoking; FEV1 < 50% predicted; use of anti-reflux medication; history of peptic ulcer disease; and clinical symptoms warranting acid suppression (symptoms more than twice a week). All participants signed written informed consent. The study was approved by all local Institutional Review Boards as listed in detail in the online supplemental information. The trial was registered at Clinical Trials.gov (NCT00069823).

Dual 24 hour pH probe testing was performed at centers with available equipment. Details of placement and interpretation have been published elsewhere.⁹ All participants completed baseline medical history questionnaires underwent pulmonary function testing and self-administered the Asthma Symptom Utility Index (ASUI)¹¹, Juniper Asthma Control Questionnaire (JAC), and a Gastroesophageal Reflux Disease Symptom Assessment Scale (GSAS)¹² at the baseline visit.

Questions pertaining to obstructive sleep apnea were added to the baseline study assessments after the first 156 participants had already been recruited to address how co-morbidities related to obesity could affect asthma control and interact with GERD. Participants evaluated for sleep disturbance therefore represent a subset of those who underwent an evaluation for GERD.

Data analysis

All analyses were performed excluding underweight participants (BMI < 18.5) enrolled in the parent study for the current analysis. Comparisons between groups (e.g. BMI categories) were made using the Kruskal-Wallis tests for continuous variables and Fisher's exact test for categorical variables. Linear regression models were used to estimate the association of markers of OSA, alone or adjusting for potential confounders, on asthma control (ASUI and JAC). Potential confounders were selected based upon prior and observed associations with OSA and asthma severity. Statistical analyses were performed using STATA 10.0 (College Station, Texas) and R (The R project for Statistical Computing, Version 2.11.1, <http://www.r-project.org/>) statistical package.

Results

A total of 402 people participated in the study of reflux treatment. We excluded 6 underweight participants with a BMI < 18.5 and one individual missing BMI data from this current analysis. 53 % of the remaining 395 participants were obese, with a BMI of 30 kg/m² or greater. Overweight and obese individuals tended to be slightly older ($p = 0.02$) and there was a higher prevalence of women in the upper BMI categories, although this was not statistically significant ($p = 0.14$). There was not a significant difference in racial representation across the BMI categories (Table 1).

Participants in the higher BMI categories had lower FVC, and less air flow obstruction (Table 1). Lung function in the cohort overall was moderately impaired in these participants with poorly controlled asthma.

Obese individuals had a higher prevalence of self-reported reflux, and increased reflux related symptoms (measured by the GSAS questionnaire) compared with leaner participants. pH probe testing showed a similar prevalence of proximal reflux in all weight categories (Table 1). Despite the fact that lean participants had a slightly lower prevalence of distal reflux, there was no difference in the prevalence of distal reflux between those who were simply overweight (BMI 25–29.9) versus those who were obese (BMI ≥ 30) (Table 1). We found no effect of gender on the prevalence of reflux (data not shown).

We determined the effect of the presence of reflux, measured by pH testing (proximal and distal probes) and self-report, on lung function, and asthma symptoms in obese participants. We found no difference in any measure of spirometric lung function or symptom scores between those obese individuals with and without reflux as defined by pH testing or patient self report (Table 2).

The subset of individuals for whom OSA data was obtained differed slightly from that of the whole cohort (Table 3). There was no significant difference in age or gender among the BMI groups. Self-report of diagnosis and symptoms of OSA were more common in patients in the higher BMI categories. 17 % of obese participants reported a diagnosis of OSA versus 0% of lean participants ($p < 0.001$).

We studied the effect of sleep disordered breathing on asthma in participants with a BMI ≥ 30 (Table 4). We excluded 8 participants who were being treated for sleep apnea, as this

could modify the effect of OSA on asthma. We observed increased asthma symptoms as measured by the Juniper Asthma Control questionnaire (JAC), and the Asthma Symptom Utility Index questionnaire (ASUI) in obese participants reporting a diagnosis OSA, although the increase was not statistically significant (Table 4). There were even stronger increases in asthma symptoms in those participants reporting witnessed apneas, which were statistically significant. No measure of OSA was associated with worsened lung function.

Linear regression was performed to determine the relationship between asthma symptoms measured by the ASUI and JAC and measures of OSA among obese patients (Table 5). We found that ASUI and JAC were worse in those reporting symptoms of OSA. Of the individual factors, witnessed apnea had the strongest association with decreased asthma control. There was a highly significant relationship between the number of symptoms of OSA reported by the participant and asthma control as measured by the JAC ($p = 0.001$, $R^2 = 0.08$) and the ASUI ($p = 0.0005$, $R^2 = 0.09$). After adjusting for lung function, race and gender, the effects were unchanged (data not shown).

Discussion

In this research study population of subjects with poorly controlled asthma, there was a very high prevalence of obesity. Patients in the higher weight categories tended to have more severe asthma as assessed by symptoms, and decreased spirometric lung volumes, though obese participants tended to have less airflow obstruction. The presence of reflux as measured by esophageal pH probe testing was common in patients of all weight categories. The prevalence of symptoms and diagnosis of OSA was increased in those with a higher BMI. Reflux was not associated with any measure of asthma severity; however symptoms of obstructive sleep apnea were associated with worse asthma control. Of common co-morbidities that occur in obesity, OSA, but not gastro-esophageal reflux disease, may contribute to poor asthma control.

Obesity is a risk factor for the development of asthma, as has been reported in numerous studies, and many different populations.^{13,14} In the United States it is estimated that obesity may be responsible for the development of 250 000 new cases of asthma per year.¹⁵

The 51% prevalence of obesity in this research patient population is considerably higher than that reported for the U.S. population as a whole. For 2008 the Behavioral Risk Factor Surveillance System reported that only 6 states had an obesity prevalence of over 30%, and the highest prevalence of obesity in any state was 32.8%.¹⁶ We do not know the reason for the higher prevalence of obesity in our patient population. It is possible that people with poorly controlled asthma are more likely to be obese than the general population. However, this was not a population based study, and there may be factors specific to this research population that led to an overrepresentation of obese asthmatics.

Obese asthmatics tended to have slightly more severe asthma as assessed by spirometric lung volumes and symptom scores, though airflow obstruction was less severe. There has been conflicting data published on the severity of asthma in patients of increasing BMI. Some reports of select patient populations have previously described no difference in asthma control and severity by BMI.¹⁷⁻¹⁹ However, many larger population based samples suggest worse asthma control in patients with a higher BMI.^{1,20,21} Our data suggest that some, but not all, measures of asthma severity are increased in the obese.

There are many abnormalities in obesity that could lead to poor asthma control; these include the mechanical effects of obesity, inflammatory factors related to abnormalities of metabolism in the obese, and also co-morbidities in the obese such as reflux and OSA. The

purpose of this study was to determine the effects of reflux and OSA on asthma in the obese in this study.

We found a high prevalence of reflux in this population, this despite the fact that participants were selected to have reflux symptoms no more than two times per week. The prevalence of reflux in this patient population was in line with previous publications on reflux and asthma.²² Reflux is common in this patient population, but does not appear to be a major factor contributing to asthma in the obese: pH probe positive reflux did not increase in proportion to BMI, and was not associated with more severe asthma. The finding that acid reflux is not a major factor contributing to asthma in the obese, is consistent with our finding in this study population as a whole: treatment of acid reflux did not improve asthma outcomes,⁸ and acid reflux was not associated with more severe asthma.⁹

OSA is another factor that has been considered in the pathogenesis of asthma in the obese. A variety of mechanisms could link sleep disordered breathing and asthma: increased vagal tone; stimulation of neural receptors in the larynx causing reflex bronchoconstriction; hypoxia induced increase in bronchial hyperreactivity; and exacerbation of metabolic factors and weight gain.²³

A number of studies have reported a high prevalence of OSA in asthma, and that obstructive sleep apnea is related to asthma severity^{24–27} Small studies suggest that treating OSA improves asthma outcomes.⁶⁷ We found that symptoms and self-report of OSA was increased in proportion to BMI, as has been reported in other studies.²⁸ We found that obese asthmatics with symptoms of OSA had increased asthma symptoms, although there was no difference in lung function abnormalities. This suggests that OSA, which is a major co-morbidity in this patient population, may contribute to poor asthma control. Another possibility is that poor asthma control may contribute to sleep disturbance: our results suggest that further study of OSA and asthma is warranted.

Our study has a number of limitations. This was not a population based cohort, which may limit the generalizability of our findings. Patients in this study had minimal symptoms of reflux, though we objectively documented acid reflux in a large number of asthmatics, and the prevalence of reflux was similar to that reported in previous studies. Nevertheless, it is certainly possible that more severe reflux may have led to different findings. We did not objectively diagnose OSA, which would have been prohibitively expensive in a study primarily designed to assess reflux, though we asked about a number of symptoms strongly associated with OSA,²⁹ and found a highly significant relationship between increasing number of symptoms of OSA and asthma control.

In summary, we have shown that a patient population selected to have poorly controlled asthma had a very high prevalence of obesity. Obese asthmatics tend to have worse asthma control and lower spirometric lung volumes. We found a high prevalence of reflux, but acid reflux did not increase in proportion to BMI, and asthma severity did not differ in those moderately obese asthmatics with and without reflux. Symptoms and diagnosis of OSA were more common in the obese and associated with worse asthma control. Future studies are required to determine if treatment of OSA could improve asthma control in the obese.

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Martin (coordinators); University of Miami, Miami–University of South Florida, Tampa: A. Wanner (principal investigator, Miami), R. Lockey (principal investigator, Tampa), E. Mendes (principal clinic coordinator for University of Miami), S. McCullough (principal clinic coordinator for University of South Florida), B. Fimbel, M. Grandstaff (coordinators); University of Minnesota, Minneapolis: M.N. Blumenthal (principal investigator), G. Brottman, J. Hagen (coprincipal investigators), A. Decker, D. Lascewski, S. Kelleher (principal clinic coordinators), K. Bachman, M. Snee (coordinators); University of Missouri, Kansas City School of Medicine, Kansas City: G. Salzman (principal investigator), D. Pyszczyński (coprincipal investigator), P. Haney (principal clinic coordinator); St. Louis Asthma Clinical Research Center: Washington University, St. Louis University and Clinical Research Center, St. Louis: M. Castro (principal investigator), L. Bacharier, K. Sumino (coinvestigators), M.E. 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Edelman (scientific consultant), S. Rappaport, G. Pezza; Project Office, National Heart Lung and Blood Institute: V. Taggart (project officer), G. Weinmann (DSMB secretary, airway branch chief); ALA Scientific Advisory Committee: G. Snider (chair), N. Anthonisen, M. Castro, J. Fish, D. Ingbar, S. Jenkinson, D. Mannino, H. Perlstadt, L. Rosenwasser, J. Samet, D. Schraufnagel, J. Smith, L. Smith, T. Standiford, A. Wanner, and T. Weaver.

Abbreviation List

GERD	gastro-esophageal reflux disease
OSA	obstructive sleep apnea

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Table 1

Comparison of demographics, lung function, asthma severity, and GERD characteristics among BMI Categories

	Normal weight BMI: 18.5–24.9 (N = 81)	Overweight BMI: 25.0 – 29.9 (N = 105)	Obese BMI >= 30 (N = 209)	P-value *
Demographics				
Age (yrs)	39 (14)	42 (14)	43 (13)	0.02
Female, N (%)	53 (63%)	64 (61%)	150 (72%)	0.14
Race, N (%)				0.74
White	45 (56%)	56 (53%)	100 (48%)	
Black	27 (33%)	39 (37%)	84 (40%)	
Other	9 (11%)	10 (10%)	25 (12%)	
Lung function				
FEV1 % predicted	78.2 (15.5)	77.3 (14.6)	76.7 (15.9)	0.52
FVC % predicted	91.9 (14.7)	89.2 (14.4)	84.7 (14.7)	< 0.001
FEV1/FVC	85.3 (12.6)	87.0 (10.8)	90.6 (10.6)	0.002
Asthma severity				
JAC	2.17 (0.77)	2.14 (0.68)	2.14 (0.84)	0.08
ASUI	0.79 (0.66 to 0.85)	0.76 (0.62 to 0.86)	0.73 (0.54 to 0.85)	0.07
GERD characteristics				
Self-reported GERD, N (%)	6 (7%)	15 (14%)	38 (18%)	0.07
pH Probe, N (%)				
Proximal GERD ⁺	19 (39%)	24 (38%)	49 (39%)	0.99
Distal GERD [‡]	17 (27%)	36 (45%)	68 (43%)	0.06
GSAS	0.33 (0.06 to 0.67)	0.33 (0.20 to 0.80)	0.53 (0.36 to 0.94)	< 0.001

Values shown are means (standard deviation), median and IQR for GSAS, or number with % where indicated.

* p value reported for kruskal-wallis test for continuous variables, and χ^2 for proportions

Definition of abbreviations: JAC is Juniper asthma control score, higher number indicative of worse control. ASUI is asthma symptom utility index, lower number indicative of worse control. GERD is Gastro-esophageal reflux disease. GSAS is Gastroesophageal Reflux Disease Symptom Assessment Scale, higher number indicative of more symptoms.

⁺ Proximal pH probe data for 49 lean, 63 overweight, 82 obese and 44 very obese individuals

[‡] Distal pH probe data for 62 lean, 80 overweight, 101 obese and 57 very obese individuals

Table 2

Association between GERD and measures of lung function and asthma severity among obese individuals (BMI ≥ 30).

pH Probe			
Proximal GERD	Negative (N = 77)	Positive (N = 49)	P-value
FEV1 % predicted	77.8 (14.4)	76.3 (17.0)	0.62
FVC % predicted	86.8 (13.1)	83.3 (15.5)	0.22
FEV1/FVC	89.7 (10.2)	91.7 (12.0)	0.32
JAC	2.26 (0.79)	2.36 (0.85)	0.57
ASUI	0.73 (0.18)	0.71 (0.22)	0.67
Distal GERD	Negative (N = 90)	Positive (N = 68)	P-value
FEV1 % predicted	74.6 (14.7)	78.5 (16.5)	0.15
FVC % predicted	83.1 (13.9)	86.3 (14.7)	0.15
FEV1/FVC	89.9 (9.6)	91.0 (11.8)	0.63
JAC	2.38 (0.89)	2.38 (0.90)	0.83
ASUI	0.71 (0.19)	0.68 (0.21)	0.80
Self-reported GERD			
	Negative (N = 171)	Positive (N = 38)	P-value
FEV1 % predicted	76.8 (16.3)	76.2 (14.5)	0.60
FVC % predicted	84.4 (15.0)	86.1 (13.0)	0.49
FEV1/FVC	90.9 (10.4)	88.9 (11.9)	0.46
JAC	2.37 (0.84)	2.33 (0.84)	0.81
ASUI	0.68 (0.20)	0.70 (0.18)	0.67

Values shown are mean (standard deviation).

Table 3

Comparison of demographics, lung function, asthma severity, and OSA characteristics among BMI categories for patients with OSA information available.

	Normal weight BMI: 18.5–24.9 (N = 50)	Overweight BMI: 25.0 – 29.9 (N = 62)	Obese BMI >= 30 (N = 133)	P-value *
Demographics				
Age (yrs)	40 (14)	41 (14)	43 (13)	0.34
Female, N (%)	35 (70%)	40 (65%)	96 (72%)	0.54
Race, N (%)				0.81
White	29 (58%)	34 (55%)	64 (48%)	
Black	17 (34%)	23 (37%)	56 (42%)	
Other	4 (8%)	5 (8%)	13 (10%)	
Lung function				
FEV1 % predicted	76.5 (16.7)	78.5 (14.1)	78.0 (16.5)	0.95
FVC % predicted	90.8 (16.6)	91.2 (14.9)	85.4 (15.5)	0.02
FEV1/FVC	84.6 (13.7)	86.7 (11.1)	91.4 (10.3)	0.002
Asthma severity				
JAC	2.22 (0.80)	2.06 (0.68)	2.35 (0.79)	0.13
ASUI	0.78 (0.66 to 0.85)	0.79 (0.74 to 0.89)	0.71 (0.55 to 0.84)	0.049
OSA characteristics				
Sleep apnea, N (%) ⁺	0 (0%)	4 (6%)	23 (17%)	< 0.001
Snoring, N (%) [‡]	25 (50%)	41 (66%)	107 (80%)	< 0.001
Witnessed apneas, N (%) ^{‡‡}	3 (6%)	8 (13%)	29 (22%)	0.02
Day time naps, N (%) ^{‡¶}	12 (24%)	12 (19%)	48 (36%)	0.04
CPAP/BIPAP use, N (%)	0 (0%)	1 (2%)	8 (6%)	0.12

* p value reported for Kruskal-Wallis test for continuous variables, and Fisher's exact test for proportions

⁺ participants responded yes/no to the question "Have you ever been diagnosed with sleep apnea?"

[‡] participants responded yes/no to the question "Have you ever been told you snore?"

^{‡‡} participants responded yes/no to the question "Has anyone ever noticed that you stop breathing during your sleep?"

[¶] Participants responded yes/no to the question "Do you often take naps during the day?"

Table 4

Association between sleep apnea and measures of lung function and asthma severity among obese individuals (BMI ≥ 30).

Sleep apnea	No (N = 109)	Yes (N = 15)	P-value
FEV1 % predicted	77.7 (16.4)	79.7 (19.7)	0.65
FVC % predicted	84.9 (15.7)	87.9 (16.3)	0.28
FEV1/FVC	91.6 (10.0)	90.2 (11.6)	0.70
JAC	2.30 (0.75)	2.73 (1.07)	0.08
ASUI	0.69 (0.20)	0.61 (0.19)	0.11
Witnessed apneas	No (N = 99)	Yes (N = 26)	P-value
FEV1 % predicted	77.1 (17.8)	81.1 (12.7)	0.17
FVC % predicted	85.2 (16.7)	85.7 (11.8)	0.79
FEV1/FVC	90.6 (10.4)	94.8 (8.7)	0.04
JAC	2.25 (0.73)	2.79 (0.93)	< 0.01
ASUI	0.71 (0.18)	0.57 (0.22)	< 0.01

Values shown are mean (standard deviation).

Table 5

Assessment of the effect of the markers of OSA on asthma symptoms among obese participants

<u>JAC</u>	Mean difference in score, β (SE)	P-value
At least one OSA marker	0.34 (0.20)	0.09
Number of markers of OSA	0.23 (0.07)	0.001
Sleep apnea	0.43 (0.21)	0.047
Witnessed apneas	0.55 (0.17)	0.002
Snoring	0.25 (0.18)	0.17
Daytime naps	0.21 (0.15)	0.16
<u>ASUI</u>	Mean difference in score, β (SE)	P-value
At least one OSA marker	-0.12 (0.05)	0.012
Number of markers of OSA	-0.06 (0.02)	0.0005
Sleep apnea	-0.07 (0.05)	0.16
Witnessed apneas	-0.14 (0.04)	0.001
Snoring	-0.10 (0.04)	0.02
Daytime naps	-0.05 (0.04)	0.18