

Clinical Implications of the Obese-Asthma Phenotypes



Jennifer Diaz, MD, Sherry Farzan, MD*

KEYWORDS

• Obesity • Asthma • Phenotypes • Body mass index

KEY POINTS

- The prevalence of obesity and asthma around the world is increasing, and together they have led to the classification of two obese-asthma phenotypes.
- The two obese-asthma phenotypes are early-onset asthma, which has an atopic quality, and late-onset asthma, with less atopic features.
- Both obese-asthma phenotypes are characterized by a severe form of asthma, with more exacerbations and poorer symptom control compared with lean asthmatics.
- The obese-asthma phenotypes are less responsive to inhaled corticosteroid and therefore new avenues for treatment should be considered, including dietary changes, weight loss, and use of nonstandard medications.
- Comorbid conditions, such as depression and obstructive sleep apnea, must be addressed as complicating factors in asthma management.

INTRODUCTION

Across the United States and the world there is an large increase in the prevalence of both obesity and asthma. The burgeoning rates of these two epidemics are occurring in the both the adult and pediatric populations. With the increased incidence of obesity and asthma, new asthma phenotypes have emerged with different characteristics, presentation, and treatment responses compared with traditionally described asthma. This article discusses these evolving obese-asthma phenotypes.

EPIDEMIOLOGY

The Obesity Epidemic

An epidemic is defined as an outbreak or product of sudden rapid spread, growth, or development, usually used in health care to describe the spread of diseases.

Disclosure: S. Farzan has received research support from the Thrasher Foundation Award # 9174, New York State Empire Clinical Investigators Program, and Merck Study #39377. J. Diaz has nothing to disclose.

North Shore-Long Island Jewish Health System, Division of Allergy and Immunology, Hofstra School of Medicine, 865 Northern Boulevard, Suite 101, Great Neck, NY 11021, USA

* Corresponding author.

E-mail address: sfarzan@nshs.edu

Immunol Allergy Clin N Am 34 (2014) 739–751

<http://dx.doi.org/10.1016/j.iac.2014.07.008>

immunology.theclinics.com

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However, because of its large increase in prevalence, obesity has reached epidemic status.

Obesity is classified using the body mass index (BMI) (Table 1). Some studies use waist circumference or percentage of body fat to determine weight classification, and this may be a better predictor of obesity-associated morbidity.¹⁻³

According to a 2008 World Health Organization survey, more than half a billion adults around the world were categorized as being obese, and more than 1.4 billion were overweight, constituting 10% of the adult population.⁴ More alarming findings exist in the United States, with the 2010 US Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination Survey (NHANES) showing more than 70 million adults and 12 million children (36% and 15%, respectively) considered obese.⁵ With the increase of obesity in the United States has come an increase in heart disease and diabetes, as well as many other diseases, including asthma.

Asthma, Asthma Everywhere

The prevalence of asthma is also increasing. In the 2000 Behavior Risk Factor Surveillance Survey (BRFSS), most states reported an asthma prevalence of less than 8.3%. By the 2010 BRFSS, 46 states reported an asthma prevalence of greater than 11.5%.⁶ According to a 2011 CDC health survey, 18.9 million adults (8.2%) and 7.1 million children (9.5%) in the United States were diagnosed with asthma. These numbers have increased by 4.3 million since 2001. Along with increasing prevalence have come increases in asthma-related medical costs, office/emergency room visits, and morbidity.⁷ Therefore, it is important for clinicians to be able to recognize modifiable risk factors for development of severe asthma, such as obesity.

RISK FACTORS

Obesity and Asthma: Are These Related?

With the increase in prevalence of both asthma and obesity, it is crucial to examine the underlying relationship. Over the last decade there have been numerous studies showing that both obese adults and children are at a significantly higher risk of developing asthma.^{3,8-10}

Pediatric population

Rodriguez and colleagues⁹ examined NHANES data from more than 12,000 children and adolescents in an attempt to identify risk factors for pediatric asthma. Children and adolescents with a sex-specific BMI of greater than the 85th percentile had an almost 2-fold increased risk for developing asthma, which was more severe and difficult to control. Compared with other groups with similar risk factors (including parental

Table 1
Weight classification based on BMI

Classification	BMI (kg/m²)
Underweight	<18.5
Normal	18.5–24.9
Overweight	25–29.9
Obese (class 1)	30–34.9
Obese (class 2)	35–39.9
Extremely obese (class 3)	≥40

atopy), those with a higher BMI had more episodes of wheezing and hospitalizations. The timing of the weight gain plays a role in a child's level of risk for developing asthma. Children who gain an excessive amount of weight over the first 6 years of life, especially during infancy, are at an even higher risk for asthma than children who gain weight later in childhood.¹¹

Adult population

The adult population shows a similar association between obesity and asthma. A meta-analysis including more than 300,000 subjects reported a 50% increase in the risk of developing asthma if the patient was obese or overweight. Among overweight individuals, the odds ratio of developing asthma was 1.32, whereas for obese individuals it was 1.92, showing a dose-response relationship between BMI and the risk of developing asthma. Similar to the pediatric population, obese asthmatics tend to develop a more severe, refractory form of asthma.^{12,13} In the adult population, it has been argued that central obesity is predictive of only nonatopic asthma.³ Published data reveal that 50% of asthmatics are obese, although it has not been established that asthma leads to obesity.¹⁴

Gender, race, and ethnicity

In examining the obese-asthma interplay, it is important to assess whether this association is mediated by sex, race, or ethnicity. Obesity seems to be a significant risk factor for developing asthma in women.^{8,15,16} However, the role of obesity in men is less certain, with conflicting results. There are numerous studies reporting that obesity does not increase the risk of developing asthma in men.^{3,16,17} In contrast, Beuther and Sutherland,¹⁰ as well as Huovinen and colleagues,¹⁸ reported that the risk of developing asthma is similar in both women and men, although there was a trend toward greater risk in women. Gender in combination with race and ethnicity could explain the inconsistent data in men. In a CDC survey from the 2000 BRFSS the obesity-asthma association was found in men, but only in Hispanic and black people.¹⁵

The role of race and ethnicity in the relationship between obesity and asthma should be examined. Similar obesity-asthma associations have been shown in Chinese, Norwegian, and Indian populations.^{19–22} Kim and Camargo¹⁵ showed the obesity-asthma association in black and Hispanic people. In the 2009 to 2010 BRFSS, obesity was determined to be a risk factor in both white and black people.²³ The Black Women's Health Study followed more than 40,000 women over 10-year and found an increased incidence in asthma in the overweight and obese population, with a dose-response relationship.²⁴ These data suggest that the association between obesity and asthma exists in a diverse population.

The controversy surrounding obesity's effect on asthma in men versus women not only exists in the adult population but also in the pediatric population. Contrary to the adult studies, many pediatric studies show a greater association of obesity as a risk factor for boys instead of girls.^{12,25} One study comparing lung function of boys and girls aged 6 to 17 years found that obese boys had significantly worse airflow obstruction compared with their normal-weight counterparts, whereas in girls obesity did not cause any difference in level of airflow obstruction compared with the normal-weight asthmatics.²⁶

In the pediatric population, a few studies have examined the role of race in the risk of asthma. One pediatric study found that, although obese Hispanic and white individuals had increases in incidence of asthma, the increase was significantly higher in Asian/Pacific Islanders and was attenuated in black individuals.¹²

PATHOPHYSIOLOGY

Obesity and Lung Function

An increase of BMI leads to airway changes independent of asthma. The most significant changes noted with increased BMIs occur in lung volumes. There are significant reductions in functional residual capacity (FRC) and expiratory reserve volume (ERV). In general, these changes only become evident when patients reach BMI greater than 30. At this level of obesity, the FRC and ERV are 75% and 45%, respectively, that of subjects with a BMI of 20. In addition, patients with BMI greater than 30 develop mild changes in total lung capacity, vital lung capacity, and residual volume.²⁷ With increased BMI, there can be proportional decreases in both the forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC),²⁸ or more profound reduction in FVC,²⁹ resulting in a normal or increased FEV₁/FVC. However, because obese individuals breathe at lower lung volumes, the resulting airway narrowing may contribute to heightened airway reactivity.^{30–33} **Table 2** presents a summary chart of lung function in obese asthmatics.

Obesity and Airway Inflammation

Obesity is a state of chronic low-grade inflammation with increased adipocyte-driven proinflammatory activity.^{34,35} Adipocytes secrete hormones, including leptin and adiponectin. These adipokines are being investigated to determine their role in inflammatory states such as asthma. In addition, there is increased secretion of tumor necrosis factor alpha, interleukin-6, plasminogen activator factor-1, and nitric oxide, as well as increased infiltration of macrophages.^{35,36} Adipokine secretion and macrophage infiltration creates systemic and local inflammation.

Several studies have determined that inflammation in obese asthmatics is not the traditional eosinophilic/T helper 2 (TH2) inflammation. This difference in the inflammatory response could explain the poor response to standard asthma therapy. Several studies have shown that increasing BMI is inversely related to sputum eosinophils, fraction of exhaled nitric oxide (Feno; a marker of eosinophilic inflammation), or both.^{37–39} In contrast, there are also studies that did not find any significant relationship between body mass index and sputum eosinophils.⁴⁰

Neutrophil-predominant inflammation is associated with difficult-to-control forms of asthma. Therefore, because obesity is associated with a more severe phenotype of asthma (discussed later), some obese asthmatics show a trend toward neutrophilic inflammation. Several studies have described a group of obese women with asthma who have neutrophil-predominant inflammation.^{41,42} In addition, there is a decrease in airway neutrophils with weight loss by both dietary changes and by exercise.⁴³

Table 2
Lung function in obese asthmatics (BMI>30)

Lung Function	Observed Effect
FRC	Decreased
ERV	Decreased
Total lung capacity	Mildly reduced
Vital lung capacity	Mildly reduced
FEV ₁ /FVC	Normal/increased
Spirometry interpretation	Restrictive

CLINICAL FEATURES

What Are Phenotypes and Cluster Analyses?

Asthma is a heterogeneous disease. The additional comorbidity of obesity adds to the complexity by creating new obese-asthma phenotypes. Phenotypes are defined as the set of observable characteristics of an organism that are produced by the interactions of the genotype and the environment.⁴⁴ In asthma, phenotypes are based on several factors, including age of onset, smoke exposure, atopy, inflammatory infiltrates, severity of disease, and response to standard medications. With a better understanding of these phenotypes, clinicians can more effectively treat this population of patients.

Cluster analysis uses multivariate mathematical algorithms to quantify similarities between individuals within a population based on multiple specific variables, and then groups individuals into clusters based on their similarities.⁴⁵ By using cluster analyses, researchers are able to objectively define these phenotypes, including the newly described obese-asthma phenotypes (Table 3).

Obese Versus Lean Asthmatics: Differences in Presentation

Cluster analyses and clinical observation have shown that obese asthmatics are not a uniform group. Several cluster analyses have identified two major groups of obese asthmatics that are categorized by age of onset of asthma symptoms as well as TH2 inflammation. These groups are designated as early-onset and late-onset obese asthma. In comparisons of both groups of obese asthmatics with their lean counterparts, more of the obese/overweight individuals take controller medications. They also had more continuous respiratory symptoms and lower quality-of-life scores than their lean counterparts.^{46–48} In the cluster analysis by Sutherland and colleagues,⁷² both obese groups had similar lung impairment, levels of adipokines, markers of systemic inflammation, and immunoglobulin E (IgE), the last of which is a differentiating factor between the two phenotypes in other analyses (discussed later).

Early-onset Obesity Associated Asthma

The early-onset group has asthma symptoms before 12 years of age with obesity playing a complicating role. The early-onset asthma affects male and female patients equally and is atopic in nature, with members of this group having increased IgE levels. They also have severely decreased airway function, significant airway hyperresponsiveness, and poor asthma control. Airway inflammation is dominated by eosinophilic infiltration with high exhaled nitric oxide levels.⁴⁷

Table 3
Obese-asthma phenotypes (early onset vs late onset)

Early-onset Asthma	Late-onset Asthma
Onset < 12 y	Onset > 12 y
Male = Female	Female > Male
Atopic	Nonatopic
Severe decrease in airway function (FEV ₁ , FVC)	Minimal airway obstruction (FEV ₁ , FVC)
Significant airway hyperresponsiveness	Less airway hyperresponsiveness
Higher symptom score	Lower symptoms score
Eosinophilic airway infiltration	Neutrophilic infiltration
High TH2 biomarkers	Low TH2 biomarkers

Late-onset Obesity Associated Asthma

In contrast, obese patients with late-onset asthma are predominantly female, presenting after 12 years of age, and lacking atopic characteristics. Pulmonary function testing shows minimal airway obstruction and less airway hyperresponsiveness, with better asthma control and lower symptom scores than the early-onset asthmatics. This phenotype has a TH2 low profile with predominant neutrophil infiltration, low IgE, and low eosinophilic infiltration.⁴⁹

Clinical Outcomes

In comparisons of the clinical outcomes of obese asthmatics with their lean counterparts, the difference is apparent. The early-onset asthmatic population required more oral corticosteroid tapers, emergency department visits, hospital admissions, intensive care unit admissions, and mechanical ventilation. In addition, they had a higher incidence of pneumonia than lean asthmatics.⁴⁷ Obese asthmatics were more likely to be classified as severe asthmatics, miss more days of work, and report continuous symptoms.¹³ In addition, obesity has a more detrimental effect on the lung function of children and adolescents compared with adults.⁵⁰

OBESE ASTHMATICS AND STANDARD ASTHMA TREATMENT

Obese asthmatics' reduced response to standard therapy makes them a particularly challenging group of asthmatics to manage. This group of patients has a reduced response to the first-line therapy for persistent asthmatics, inhaled corticosteroids, which leads them to present with more difficult-to-control asthma. Peters-Golden and colleagues⁵¹ showed that patients on beclomethasone with higher BMIs had less asthma control days (ACD), whereas the number of ACD did not decrease with increasing BMI in patients on montelukast. When treated with budesonide, the normal-weight group in another study had a more significant reduction in F_{ENO} as well as symptom improvement compared with the overweight group ($\text{BMI} > 25 \text{ kg/m}^2$). There was no significant difference in airway hyper-reactivity as examined by the methacholine provocation concentration (PC₂₀) which reduces FEV₁ by 20%.⁵²

In a post-hoc analysis of data from multiple clinical trials, in both the obese and non-obese groups, fluticasone in combination with salmeterol provided better asthma control than fluticasone alone in more than 1200 patients with moderate asthma. The obese group continued to have poorer asthma control with these controllers compared with the normal-weight group.⁵³ In comparisons of inhaled corticosteroid (ICS), ICS/short acting beta agonist (SABA), and montelukast, ICS and ICS/SABA were more effective in asthma treatment than montelukast.⁵⁴ The effectiveness of low dose theophylline as add-on treatment in asthma (LODO) trial, with a cohort of 488 women, of whom 47% were obese, examined differences in presentation and response to add-on treatment with placebo, montelukast, or theophylline. With add-on theophylline, obese asthmatics had a trend toward more frequent asthma exacerbations compared with lean asthmatics. There was no difference with montelukast treatment.⁵⁵ None of the studies examining the response to controller medications among obese asthmatics has stratified them into the two phenotypes: early versus late onset of asthma.

TREATMENT OPTIONS FOR OBESE ASTHMATICS

Weight Loss

Because of the limited effectiveness of standard forms of medical therapy, new avenues for managing obese asthmatics must be explored. If obesity is a contributing

risk factor for not only development but also severity of disease, then weight reduction is an obvious approach to preventing and treating asthma in this population. Weight is one of the only modifiable risk factors for asthma. There are multiple studies of value of dietary and surgical weight loss for improved asthma outcomes.^{56–64} The results have been mixed but encouraging and are reviewed in detail elsewhere in this issue.

Role of Diet in Asthma Development and Control

In obese asthmatics, the specific contents of the diet, including fats, sugar, and low nutrients, may contribute to the chronic inflammatory state. Even a single high-fat meal has an immediate effect on inflammatory cells as well lung function. In one study, patients were given 1 high-fat meal and were monitored for 4 hours. There was a significant decrease in the response to bronchodilators as well as a rapid decrease in FEV₁/FVC ratio after the high-fat meal. In addition, sputum showed an increase in airway neutrophils.⁶⁵ This finding is consistent with previously discussed studies that found a neutrophil-predominant inflammation in obese asthmatics.

There have been several studies of the use of dietary supplementation or alteration as a means to develop better asthma control. Cochrane Reviews examining the role of supplementation with vitamin C, selenium, and low-salt diets have shown no promising evidence for benefits on asthma symptoms.^{66–68} Vitamin C may have some indication for exercise-induced asthma, but its use must be assessed further.⁶⁸ At present, there is a clinical trial (Dietary Approaches to Stop Hypertension [DASH]) of the efficacy of diet as an adjunct therapy to standard adult therapy in uncontrolled asthmatics. The DASH diet encompasses fresh fruit, vegetables, nuts, and antioxidant nutrients (vitamins A, C, E; and zinc).⁶⁹ In addition, vitamin D has been hypothesized to play a role in the interplay between obesity and asthma. Vitamin D levels are inversely correlated with BMI and with asthma severity,^{70–72} and higher serum levels are associated with improved in vitro sensitivity to glucocorticoids.⁷²

The Mediterranean diet has also proved in many studies to have protective effects on both asthma and allergic rhinitis.^{73–76} One cross-sectional study examined 174 adults with asthma and defined the patients as controlled and uncontrolled asthmatics using FEV₁, FeNO, and asthma control questionnaire (ACQ). Diet was analyzed using the alternate Mediterranean Diet Score (aMED). Controlled asthmatics had a higher aMED score, greater intake of fresh fruit, and lower ethanol intake compared with the uncontrolled asthmatics. Asthmatics who adhered to a Mediterranean diet had a 78% reduced risk of having uncontrolled asthma.⁷⁵ However, the role of diet and nutrition in development of asthma remains controversial and is reviewed in greater detail elsewhere in this issue.

Old Medications, New Use

With the complicated nature of the obese-asthma phenotypes and resistance to standard asthma therapy, new treatments must be evaluated. Statins, which are prescribed for hyperlipidemia, have been found to have antiinflammatory effects, prevent remodeling of lung tissue, and improve lung function.^{77–79} There have been varying results of the efficacy of statins in asthma, but the key may be in the selection of the patient population that will benefit from this form of treatment. A recent study hypothesized that it was the severe asthmatics, most of whom were obese, that would benefit from statins as an add-on therapy. This retrospective study examined 165 adult patients, who were divided into 2 groups: those on statins (who were mostly female and obese) and those not on statins. Their charts were examined for asthma control test (ACT) scores as a primary measure of asthma control.

Patients who were on statins had significantly increased ACT scores compared with their counterparts. This finding remained true even when comorbidities like gastroesophageal reflux disease (GERD), obstructive sleep apnea (OSA), and smoking were accounted for.⁸⁰

COMORBID CONFOUNDERS IN OBESE ASTHMATICS

It is difficult to isolate obesity and asthma from other associated comorbidities that are common in obese patients, such as GERD, OSA, and depression.^{39,81} GERD was previously thought to be a contributor to asthma symptoms, but in several studies, including a Cochrane Review, GERD treatment did not produce improvement in asthma symptoms.^{82,83} In obese asthmatics, it may be OSA but not GERD that contributes significantly to poor asthma control.⁸⁴ OSA^{84,85} and depression^{86,87} are known to contribute to poorly controlled asthma. Obese individuals with depression or anxiety have the highest risk (odds ratio, 2.93) of incident asthma compared with other groups in a prospective study of more than 20,000 adults.⁸⁸ Although these conditions may be associated with asthma-like symptoms, their presence does not fully explain the creation of this obese-asthma phenotype. Instead, these comorbidities may contribute to additional barriers in the complete management of symptoms. Because of the complexity of the conditions involved, obesity-associated asthma is a multifaceted condition requiring a multidisciplinary approach when developing a treatment plan (Fig. 1).

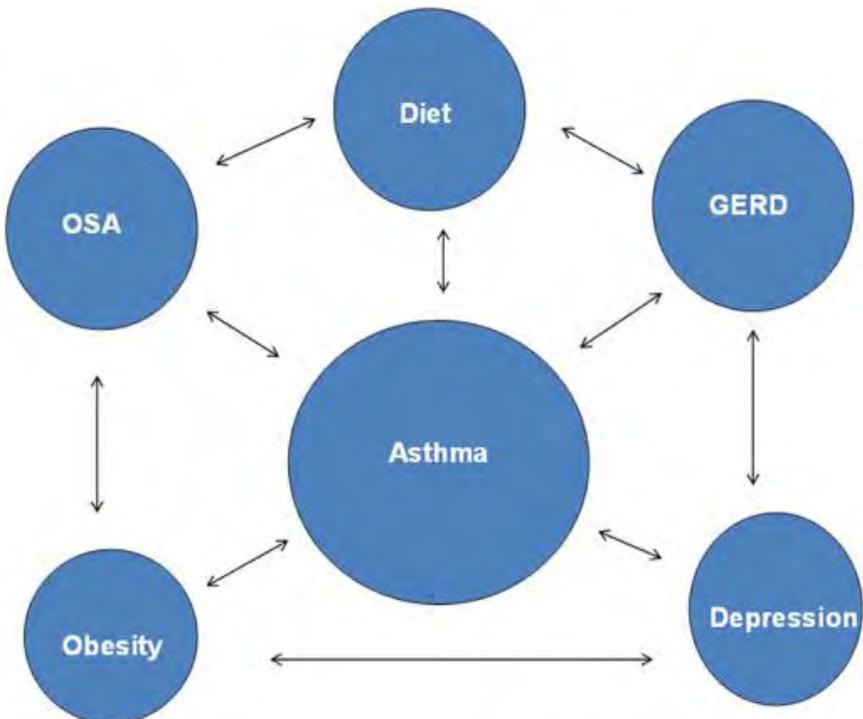


Fig. 1. The interplay between asthma and its comorbid conditions plays a significant role in the management of the obese asthmatic patient.

SUMMARY/FUTURE CONSIDERATIONS

The increasing incidence of obesity and asthma has led to the development of 2 newly defined obese-asthma phenotypes, each characterized by the age of onset of asthma. Both groups of obese asthmatics have symptoms that are more difficult to control than those of lean asthmatics. Members of the late-onset group are more likely to be nonatopic. In order to provide better treatment of these patients, physicians must be able to recognize the barriers involved in managing their asthma. These issues include, most significantly, resistance to inhaled corticosteroids as well as the additional complexity of comorbid conditions. Treatment plans need to be multidisciplinary, including asthma therapy, weight management, dietary changes, and mental health care.

With the help of cluster analyses clinicians are just beginning to make progress in understanding obese asthmatics. More knowledge about what characterizes these phenotypes, as well as an in-depth understanding of the underlying pathophysiology, or endotype, will allow more effective and personalized forms of asthma treatments to be developed. At present, there are investigations examining the role of adiponectin and leptin in the pathogenesis of this phenotype. In the future, there may be treatments to modulate adipokine levels or activity in order to obtain better asthma control. Investigators should assess how another comorbidity of obesity, diabetes, may affect the severity of asthma and prospectively examine the protective, antiinflammatory potential of some common diabetes and cardiac medications in refractory asthmatics. Furthermore, an interesting subpopulation to study would be the elderly, in whom many of these comorbidities converge. Futures studies focusing on obese asthmatics should differentiate the two distinct phenotypes, early-onset versus late-onset asthma, associated with obesity, while studying the underlying pathophysiology and determining the effectiveness of alternative treatments.

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