

The Asthma–Obesity Epidemic

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ABSTRACT: Obesity is a risk factor for the development of asthma. Understanding this link between obesity and asthma has major public health implications for developing strategies to prevent the development of asthma and to guide the management of such patients. Obese patients with asthma experience poor asthma control, worse asthma-specific quality of life, and limited response to corticosteroids. This review provides a succinct summary of the current body of literature on the epidemiological relationship between asthma and obesity, the different phenotypes of asthma in obesity, and data on the efficacy of weight loss and discusses the potential role of primary prevention efforts for the current asthma epidemic.

KEYWORDS: asthma, obesity, weight loss

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Introduction

Globally, >1 billion adults are overweight and the numbers are rising.¹ Obesity, defined as a body mass index (BMI) >30 kg/m², has long been recognized as a risk factor for chronic diseases, such as diabetes, hypertension, and atherosclerosis, and has recently been recognized as a major risk factor for asthma. Approximately 38%–50% of current adult asthmatics are obese, and ~60% of patients with severe asthma are obese.¹ It is estimated that 250,000 obese people per year in the United States are diagnosed with asthma.^{2–4} While the relationship between obesity and asthma is alarming because of the number of people affected, what makes this even more concerning is the fact that asthma among the obese is characterized by worse asthma control, decreased response to asthma medications, and higher rates of healthcare utilization.^{5–10} Obesity is associated with severe, difficult-to-control asthma.

In this review, we focus on: (1) the epidemiology linking obesity and asthma, (2) the phenotypes of asthma in obesity, (3) the impact of obesity on lung function and airway physiology, and (4) the current knowledge about the effects of weight loss on asthma control in obese individuals.

Epidemiology of Asthma and Obesity

A large number of cross-sectional studies have found associations between asthma and obesity. Seidell et al first described an association of obesity with asthma in a Dutch cohort study in 1986.¹¹ The National Health and Nutrition Examination Survey III (NHANES III) showed a strong association between asthma and BMI.¹² Several large population-based cross-sectional and case–control studies have shown a consistent and positive association between

obesity and asthma. Although the majority of these studies were conducted in Caucasian populations, similar associations have been reported within other racial and ethnic groups and among children as well as adults.^{13–21} Obesity is strongly associated with asthma across all demographic groups.

Cross-sectional studies only show that two diseases are associated, but do not inform as to which disease comes first. It seems possible that the use of corticosteroid medication and/or impaired exercise tolerance might predispose toward developing obesity among patients with asthma. However, longitudinal studies suggest that obesity precedes asthma: obesity is a risk factor for the development of incident asthma. The Nurse's Health Study II, which included 85,911 women between 26 and 46 years, found 1596 new cases of asthma developing over four years³: there was a positive, dose-dependent risk of developing asthma with increasing BMI. Huovinen et al found that obese people had a substantially higher risk of developing asthma than their lean counterparts in a nine-year follow-up of 9671 adult Finnish twins.²² NHANES I followed up 9456 participants; there was a moderately increased risk of developing asthma in obese adults aged 25–74 years who entered the study between 1971 and 1975.²³ The relative risk of developing incident asthma in people who are obese ranges somewhat between studies from 1.0 to 3.0, with a higher risk attributed to a higher level of BMI.

Phenotypes of Asthma in Obesity

Asthma is a heterogeneous disease. The clinical spectrum of disease, inflammatory milieu, demographic characteristics, and comorbidities vary and produce quite distinct phenotypes of the disease. Asthma in the obese also includes distinct



Table 1. Characteristics of asthma–obesity phenotypes.

LATE ONSET ASTHMA OBESITY	EARLY ONSET ASTHMA OBESITY
Late onset	Early onset
Non atopic	Evidence of atopy
Low markers of TH ₂ /eosinophilia	TH ₂ driven inflammation/increased airway wall eosinophilia
Increase evidence of systemic inflammation caused by obesity related cytokines	
Weight gain increases asthma severity ⁴	
Increased airway closure improved with weight loss	

phenotypes, and these are likely related to the unique pathophysiology of airway disease in obese patients.

It has long been recognized that a later-onset form of asthma, particularly common in obese women, represents a phenotype of asthma in obesity. Haldar et al performed a cluster analysis of three populations of asthmatics (asthma managed in the primary care, refractory asthma managed in secondary care, and refractory asthma managed in tertiary care): obese and predominantly female subjects with asthma were identified as having increased symptoms, later age of onset of asthma, and lower levels of atopy and eosinophilic airway inflammation (as determined indirectly by exhaled nitric oxide levels) compared with other asthmatic patients.²⁴ An analysis by the National Institutes of Health-sponsored Severe Asthma Research Program identified a similar group of obese, predominantly female asthmatics with a late age of disease onset.²⁵

Our understanding of obese asthma phenotypes has evolved since these earlier reports. Our own group identified two groups of asthmatics in patients undergoing bariatric surgery: one group had later-onset asthma and low IgE, and this group has significant improvement in airway reactivity with weight loss; the second group had earlier-onset disease and high IgE, and variable improvement in airway reactivity with weight loss.²⁶ Similar groups have emerged from other studies. Using a cluster analysis approach, Sutherland et al identified two phenotypes of asthma in obesity.²⁷ Holguin et al divided participants according to the age of onset of asthma and identified two distinct phenotypes of asthma in obesity: earlier-onset disease with higher IgE and worse asthma control, and later-onset asthma with lower IgE and better asthma control.²⁸ At least two phenotypes of asthma occur in obese patients: one is likely asthma complicated by obesity (earlier-onset disease with higher levels of markers of allergic inflammation), and the other is likely asthma consequent to obesity (later-onset disease with low levels of markers of allergic inflammation; Table 1).^{4,29–32}

Asthma Control and Severity in Obesity

Many studies have reported about asthma severity, control, and disease burden among obese asthmatics.^{27,29,33} Both functional impairment (asthma control) and risk of

complications increase in obese patients. Impairment related to asthma can be measured by the frequency of symptoms, severity of symptoms, and functional limitation. This impairment can be assessed by lung function (forced expiratory volume in one second, FEV₁), variability in peak flow, and symptoms [assessed with validated questionnaires such as the Asthma Control Test (ACT) and Juniper’s asthma control questionnaire].^{34,35} Risk of complications is typically determined by the rate of exacerbations and hospitalizations.³⁶ Studies suggest that asthma control is worse, and severity is increased in obese patients.

Schatz et al used the ACT questionnaire to examine factors associated with asthma control in 570 patients aged 35 years and older enrolled in a large managed health-care organization. In a multiple linear regression analysis, a higher BMI was an independent predictor of poor asthma control (*P* = 0.01).³⁷ Demoly et al studied 2337 Europeans with self-reported physician diagnosis of asthma and used the ACT questionnaire to measure asthma control: 30% of those with poor asthma control versus 22.7% with well-controlled asthma (*P* < 0.001) were obese.³⁶ Taylor et al studied 3095 outpatient adult asthmatics in four different states and found that obese subjects were more likely to report continuous symptoms, missed work days, and to experience persistent asthma symptoms despite use of short-acting beta agonist and inhaled corticosteroids.³⁸ These studies are consistent in that they suggest worse asthma control in obese patients.

Asthma exacerbations are also increased in obese patients. Mosen et al studied both asthma control and severity using the Asthma Therapy Assessment Questionnaire, self-report of the number of asthma-related hospitalizations in the previous year, and Juniper’s mini-Asthma Quality of Life Questionnaire: obesity was significantly associated with poor asthma control, poor asthma-specific quality of life, and asthma-related hospitalizations. Obese asthmatics had a 4.6-fold increased risk of hospitalization for asthma.⁷ Most studies suggest that obesity is associated with poor asthma control and severe diseases.

Response to Treatment

Altered response to medications in obesity has been reported in a number of studies (Table 2).^{8–10,39–42} Peters-Golden et al

**Table 2.** Studies comparing the response to therapy in overweight and obese asthmatics.

STUDY	SUBJECTS	THERAPY	RESULTS
Peters-Golden 2006 ⁸	3073	Montelukast, Beclomethasone, placebo	Reduced asthma control days with increasing BMI with use of inhaled corticosteroid. No difference with Montelukast.
Dixon 2006 ³⁹	488	Theophylline, Montelukast, placebo	Increased risk of exacerbation in obese individuals treated with Theophylline. No difference Montelukast treatment groups.
Boulet 2007 ⁹	1242	Fluticasone versus Fluticasone with Salmeterol	Fluticasone combined with Salmeterol was superior to Fluticasone alone in achieving asthma control. Reduced effectiveness was seen in both therapies, in obese subjects in comparison to their lean counterparts.
Rodrigo 2007 ⁴⁰	426	Comparing emergency department stay and rate of hospitalization	Overweight and obese subjects had significant increases in length of emergency stay and rate of hospitalization.
Sutherland 2008 ¹⁰	45	Glucocorticoid response in vitro	Decreased in vitro response to glucocorticoids in obese subjects.
Sutherland 2010 ⁴¹	1052	Fluticasone and Montelukast	Across all BMI groups, Fluticasone had greater improvements compared to Montelukast.
Farah 2011 ⁴²	49	Fluticasone and Salmeterol	Similar improvements in asthma control and lung function across all BMI groups.

first reported altered response to medication in pooled data from the studies of montelukast and inhaled corticosteroids for the treatment of asthma: response to inhaled corticosteroids decreased with increasing BMI.⁸ A reduced response to both inhaled corticosteroids and combination therapy (with fluticasone–salmeterol) was also described by Boulet and Franssen in data pooled from five studies of fluticasone, and fluticasone–salmeterol combination therapy: obese participants were less likely to achieve asthma control with these therapies. We have found altered response to theophylline: in a retrospective analysis of add-on therapy for poorly controlled asthma, obese patients tended to have increased exacerbations and worse asthma control compared with lean patients.³⁹ Obesity is associated with decreased response to standard controller therapies for asthma.

This impaired response to therapy seems also important in patients with asthma exacerbations. Rodrigo and Plaza performed a cross-sectional study of 426 asthmatics presenting to the emergency department with asthma exacerbations, 163 of whom were classified as obese/overweight: obese asthmatics had reduced response to therapy, which included systemic steroids and albuterol. Overweight and obese individuals were also more likely to be hospitalized for their asthma.⁴⁰ The cause for the decreased response to corticosteroids in obesity is poorly understood. It may be that these patients often have lower levels of the type of allergic inflammation that responds to corticosteroids. Another possible explanation is cellular resistance to corticosteroids. Sutherland et al studied in vitro cellular response to corticosteroids and found impaired induction of mitogen-activated protein kinase phosphatase-1, a signaling molecule that mediates some of the anti-inflammatory responses to corticosteroids.⁴¹ Impaired response to therapy in obese asthmatics is likely related to both resistance to

corticosteroids at a cellular level and altered mechanisms of disease in obesity.

Effect of Obesity on Lung Function

Obesity has effects on lung function that can impact respiratory mechanics independent of its effect on asthma. As such, it is not hard to anticipate that the presence of obesity itself may exaggerate the effects of existing airway disease.²¹

Although BMI is a convenient and widely accepted measure of adiposity, obesity is a heterogeneous disease, and so BMI may not be the best measure of the effect of obesity on the lung. Two distinct patterns of obesity are recognized in the general population: central and peripheral obesities. Central obesity refers to increased adipose tissue in the anterior chest wall, anterior abdominal wall, and visceral organs and is associated with cardiovascular diseases, type 2 diabetes mellitus, and the metabolic syndrome. Peripheral obesity refers to adiposity located peripherally in the subcutaneous tissue. There is evidence to suggest that the mechanical effect of obesity on lung function is more strongly associated with central body fat distribution, as determined by the waist-to-hip ratio of ≥ 0.950 .^{43–45}

The presence of adipose tissue around the chest wall, diaphragm, and abdomen restricts ribcage movement leading to reductions in lung volumes and restrictive pulmonary function.⁴⁶ Chen et al found that each kilogram of weight gain was associated with a reduction in forced vital capacity of 27 mL and FEV₁ of 23 mL in men, and 14 and 9 mL in women.⁴⁷

The functional residual capacity (FRC; the volume of air in the lung at the end of a tidal exhalation) decreases with increasing BMI; this is particularly associated with thoracic and abdominal adiposity.⁴⁸ This low FRC increases expiratory flow limitation and airway closure during normal breathing.



Early closure of airways in the dependent areas of the lung during normal breathing contributes to ventilation perfusion defects and hypoxemia in obesity.^{49,50}

Decreased lung volumes increase airway reactivity,⁵¹ perhaps through effects on airway smooth muscle.⁵² The tendency toward early airway closure may also manifest during bronchoconstriction^{53,54} and contribute to the increased dyspnea symptoms reported by obese asthmatics in comparison to their lean counterparts. We have found that obese asthmatics tend to have a less compliant lung periphery, which improves with weight loss.⁵⁴ The cause of this stiff periphery is not known, but could be related to airway closure, as sensitivity to airway closure decreases with weight loss.⁵⁵ Changes in lung function with decreased lung volumes and increased airway closure likely contribute significantly to the development of poorly controlled asthma in obesity.

Obesity and Associated Comorbidities

Obesity increases the risk of other chronic illnesses, which may also affect asthma. This includes obstructive sleep apnea. A number of studies suggest that obstructive sleep apnea is associated with poor asthma control^{56–58} and neutrophilic airway inflammation.⁵⁷ One study found that asthma was actually a risk factor for the future development of obstructive sleep apnea, independent of BMI,⁵⁹ suggesting a pathogenic and possible bidirectional link between these two diseases. It is not known if effective treatment of asthma can prevent the development of obstructive sleep apnea, though some small studies suggest that effective treatment of sleep apnea may improve asthma control.^{60,61}

Evidence that Weight Loss Improves Asthma Control

A few studies have examined if weight loss improves asthma outcomes.⁶² A summary of these studies is described in Table 3.^{63–69} Although the quality and sample size of

these studies vary, the majority of these studies have found improvements in asthma-related quality of life, lung function, and symptom scores with significant weight loss.^{62,63} Weight loss studies have included surgery, low calorie diets, exercise, and combined diet–exercise interventions.

Stenius-Aarniala et al performed a randomized parallel group study of obese asthmatics, investigating the effects of an eight-week-supervised weight reduction program on lung function, symptoms, and health status. A significant improvement was observed in individuals in the intervention group in lung function (FEV₁, FVC), symptoms, morbidity, and health status.⁵⁴ Bafadhel et al examined 151 adults with severe asthma in a one-year observational study. After 12 months, 23% of the patients had lost weight (an average of 2.8 kg), and a significant correlation was observed between weight loss and increased FEV₁, whereas no significant association was found between weight change and self-reported asthma control and exacerbations.⁷⁰ Johnson et al evaluated an alternate-day, low-calorie diet. Nine of 10 subjects adhered to the diet for an eight-week period with a mean weight loss of 8% of body weight. Improvements were seen in asthma symptoms, quality of life, peak flow, and markers of oxidative stress and inflammation.⁶⁴ More recent studies published by Pakhale et al,⁶⁵ Scott et al,⁶⁶ and Ma et al⁶⁸ implementing weight loss in the form of liquid diet (Pakhale), or diet and exercise (Scott and Ma), suggest improved asthma outcomes in patients who lose a significant amount of weight. There appears to be a threshold for improving asthma symptoms, with a 5%–10% loss of body weight required to significantly improve asthma control.

Significant weight loss can improve asthma control; conversely, significant weight gain worsens asthma control. Haselkorn et al studied the effect of weight change over a 12-month period on asthma control in patients with severe or difficult-to-treat asthma: asthma patients with a weight gain of 2.27 kg reported worse asthma control and quality of life

Table 3. Nonsurgical weight loss and asthma control.

AUTHOR, YEAR	INTERVENTION	N	WEIGHT LOSS IN INTERVENTION GROUP	EFFECT ON ASTHMA
Stenius-Aarniala 2000 ⁶³	8 weeks low calorie diet	19 adults	14.5%	Significant improvement asthma symptom scores, exacerbation rate, lung function.
Johnson 2007 ⁶⁴	8 weeks alternate day calorie restriction diet	10 adults	8%	Improvement in asthma control, QoL, lung function.
Hernández Romero 2008 ⁶⁹	Low calorie diet including meal replacements versus low calorie diet	96 adults	10.6% and 6.1% respectively	Improved symptoms, decrease medications.
Scott 2013 ⁶⁶	Diet and exercise (controlled study)	28 adults	8.5%	Improved asthma control.
Dias-Júnior 2014 ⁶⁷	Diet and weight loss medication (controlled study)	22 adults	7.5%	Improved asthma control and reduced use of rescue medications.
Ma 2014 ⁶⁸	Diet and exercise (controlled study)	330	4.1%	Improved asthma control in subjects who lost >5% of body weight.
Pakhale 2015 ⁶⁵	Liquid meal replacement	22	19%	Significant improvement in AHR and asthma control.

**Table 4.** Surgical weight loss and asthma control.

AUTHOR, YEAR	STUDY DESIGN	N	EFFECT ON ASTHMA
Reddy 2010 ⁷²	Retrospective cohort: patients with physician diagnosed asthma followed 1 year after bariatric surgery	257	At 1 year, there was significant reduction in the number of patients using oral corticosteroids, daily inhaled corticosteroids, inhaled bronchodilators. 40% of these patients became medication free.
Dixon 2011 ²⁶	12 month prospective observational study	23	Asthma control and quality of life improved at 1 year follow up. Airway responsiveness improved in patients with normal IgE levels, suggesting atopic status influences degree of response.
Lombardi 2011 ⁷³	12 month prospective observational study	14	Only exhaled nitric oxide decreased during follow up.
Maniscalco 2008 ⁷⁴	12 month prospective observational study	12	Improvements in self reported asthma control, lung function, use of rescue medications.
Boulet 2012 ⁷⁵	12 month prospective observational study	12	Significant improvements in airway hyper-reactivity, FEV ₁ , FVC, FRC, FRC/TLC and ERV. Asthma symptoms total scores were also significantly reduced with 10 patients being able to stop all asthma drugs.
van Huisstede 2012 ⁷⁶	12 month prospective observational study	28	Improvement in lung function, asthma control and quality of life in patients with asthma and morbid obesity after 12 months.
van Huisstede 2015 ⁷⁷	12 month prospective observational study	27	Bariatric surgery improved small airway function, decreased systemic inflammation and number of mast cells in the airway wall.
Hasegawa 2015 ⁷⁸	Self-controlled case series study: Obese patients with asthma s/p bariatric surgery	2261	Substantial decrease in rate of ED visit or hospitalization for asthma exacerbation at 24 months after bariatric surgery.

and required more courses of systemic corticosteroids. This study demonstrated that weight gain is associated with worse asthma outcomes and that strategies to prevent weight gain especially in severe asthmatics may lead to improved asthma control.⁷¹

There have been multiple uncontrolled studies analyzing the effects of bariatric surgery on various comorbidities, including asthma. A summary of these studies are listed in Table 4.^{26,72–77} In a large retrospective study, Reddy et al reported significantly decreased asthma medication use 12 months after surgery. Additionally, patients who experienced the least amount of weight loss (those following the laparoscopic adjustable gastric bypass banding rather than gastric bypass surgery) experienced the least improvement in asthma.⁷²

We performed a prospective study of asthmatics undergoing bariatric surgery: one year after surgery, patients with asthma experienced significant improvements in terms of asthma control, asthma-related quality of life, lung function, and airway hyperresponsiveness to methacholine.²⁶ Similarly, Boulet et al performed a prospective study involving 23 obese asthmatic subjects, of whom 12 underwent bariatric surgery. Patients who underwent bariatric surgery had significant improvements in airway reactivity, pulmonary function, and asthma control.⁷⁵

In a recent publication, Hasegawa et al reported a self-controlled case series study of 2261 obese patients with asthma, who underwent bariatric surgery. The study demonstrated that bariatric surgery was associated with a significant decrease in

the risk of emergency department visit or hospitalization for asthma exacerbation at 24 months postsurgery.⁷⁸

Implications of the Relationship Between Asthma and Obesity

Asthma is one of the most common chronic diseases in the world, and the fact that obesity is now a major risk factor for the development of this disease is a major public health issue. There is a distinct paucity of studies addressing whether strategies to prevent the development of obesity could have a meaningful impact on the development of asthma. Obesity is a complex disease characterized not only by deposition of excess adipose tissue but also with profound changes in diet and activity, which could also affect the development of asthma. It is possible that customized dietary interventions could prevent the development of this disease. Studies in pregnant mice suggest that a low-fiber diet (common in obesogenic diets) increases the risk of developing allergic asthma through the effects on the gut microbiome and immune cell development,⁷⁹ whether increasing dietary fiber content might be effective for the prevention of asthma is not known. A high-fat diet is commonly linked to obesity, and consumption of a high-fat diet can increase airway inflammation in patients with asthma⁸⁰; whether altering the fat composition of the diet might prevent the development of asthma and/or improve asthma control is not known. Decreased physical activity is often associated with the development of obesity, and studies in mice suggest that exercise can ameliorate airway



inflammation and airway reactivity,^{81,82} though increasing physical activity might be effective for the prevention of asthma is not known.

Preventing the development of asthma associated with obesity through dietary interventions and increasing physical activity has the potential to have a major impact on this epidemic, though there are very few studies addressing this issue at the present time.

Conclusion

While there is much to understand regarding the mechanisms linking obesity and asthma, weight gain leads to the development of asthma and causes more severe asthma in those with preexisting diseases. Significant weight loss appears to improve asthma control, while weight gain worsens asthma control. Losing significant amounts of weight is difficult, but can be achieved with bariatric surgery that significantly improves asthma control and reduces asthma exacerbations. However, given the expense and morbidity associated with surgical weight loss procedures, it is unlikely an optimal therapy for many obese asthmatics. Weight loss, or at a minimum avoidance of weight gain, should be a goal for patients with asthma. Given the significant data to support the benefits of asthma control and quality of life with significant weight loss, and the adverse effects of weight gain, lifestyle counseling should be a part of treatment of obese asthmatics.

A study from the Behavioral Risk Factor Surveillance System reported that only 37% of obese asthmatics reported receiving weight loss advice as part of their asthma management.⁸³ This statistic is something to be improved upon.

Author Contributions

Wrote the first draft of the manuscript: SK. Contributed to the writing of the manuscript: SK, AED. Agree with manuscript results and conclusions: SK, AED. Jointly developed the structure and arguments for the paper: SK, AED. Made critical revisions and approved final version: SK, AED. All authors reviewed and approved of the final manuscript.

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