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Obesity in Asthma: Approaches to Treatment

Shyamala Pradeepan, MBBS, MD, MRCP, FRACP¹,

Lookout Road New Lambton NSW 2305 Australia Phone: 61249223150 Fax: 61249223160
shyamala.pradeepan@hnehealth.nsw.gov.au

Garth Garrison, MD², and

Given D208 89 Beaumont Avenue Burlington, VT 05405 Phone: 802 656 3525 Fax: 802 656
3525 garth.garrison@vtmednet.org

Anne E. Dixon, MA, BM, BCh²

Given D208 89 Beaumont Avenue Burlington, VT 05405 Phone: 802 656 3525 Fax: 802 656
3525 anne.dixon@vtmednet.org

¹Department of Respiratory and Sleep Medicine, John Hunter Hospital Newcastle, NSW, Australia

²Department of Medicine, University of Vermont, Burlington, Vermont, USA

Abstract

There is mounting evidence that obesity is associated with asthma, both of which are seeing a dramatic increase in prevalence. Not only is obesity a risk factor for the development of asthma, it is also associated with poor asthma control. Asthma phenotypes associated with obesity include early-onset allergic asthma and late-onset non-allergic asthma. The pathogenesis of the linkage is complex; obesity causes a variety of mechanical, metabolic, and immunological changes that can affect the airways. The treatment of asthma in obesity can be challenging as obesity is associated with poor response to standard controller medications. A tailored approach that involves combining pharmacologic and non-pharmacologic therapies including weight loss, dietary interventions and exercise, along with identification and treatment of obstructive sleep apnea should therefore be considered in this population.

Keywords

Asthma; Obesity; Lung function; Inhaled corticosteroids; Leukotrienes; Gastroesophageal reflux disease; GERD; Obstructive sleep apnea; Treatment; Weight loss; Exercise; Comorbidities

Introduction

The prevalence of obesity has increased dramatically throughout the world, and particularly in the United States (1). Obesity is a major risk factor for asthma: those overweight (BMI 25-25.9 kg/m²) and obese (BMI ≥ 30 kg/m²) are 38% and 92% respectively more likely to develop asthma compared to those with normal weight (2). As such, it is estimated that obesity leads to 250,000 new cases of asthma per year in the U.S. (2). Obesity is leading to a new epidemic of asthma. Not only is obesity a risk factor for asthma, but obese patients tend to have poor asthma control (3, 4), with one study suggesting that obese asthmatics have a

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nearly five-fold risk of hospitalization due to asthma exacerbations compared with lean asthmatics (5). Obesity, therefore, is changing the nature of the asthma throughout the world. The purpose of this article is to provide an evidence based framework for the treatment of asthma in obesity. We will first review what is known about the basic pathophysiology of asthma in obesity, before discussing the role of medications and non-medication based approaches that may be useful for the treatment of asthma in obesity.

Pathophysiology of asthma in obesity

Obesity leads to a number of changes in normal lung physiology and immune function which have an important impact on the pathogenesis of lung disease in this population.

Obesity fundamentally alters lung mechanics. The obese breathe at a lower resting lung volume than lean asthmatics because of the loading effects of adipose tissue on the chest wall, and of visceral adipose tissue on the diaphragm (6). As the expiratory reserve volume decreases, the functional residual capacity frequently approaches the residual volume in the very obese. Breathing at low lung volumes, even in normal non-asthmatic volunteers, can induce airway hyperresponsiveness (7, 8). The reasons for this mechanical effect on airway reactivity are likely to be complex. One hypothesis suggests that decreased loading of airway wall smooth muscle at lower lung volumes may allow for increased actin-myosin crosslinking at the molecular level (9). This would make the muscle stiffer, more resistant to lengthening, and therefore tend to reduce the caliber of the open airway. This mechanical effect of obesity on airway function is unlikely to respond to conventional medical therapy, but as outlined later in this article, may respond to other therapies such as weight loss or perhaps even continuous positive airway pressure.

Adipose tissue produces mediators that can have direct effects on the airway. Adipose is a metabolically active tissue that elaborates a number of cytokines and adipokines recognized to have a role in the pathogenesis of co-morbidities of obesity such as the metabolic syndrome (10). These mediators likely also play a role in the development of lung disease in obesity. Shore *et al* have shown that the adipokine leptin (which is increased in obesity) can augment airway reactivity even in lean mice (11). We have shown that airway epithelial cells bear receptors for leptin, and that visceral leptin levels are significantly related to airway responsiveness in obesity (12). The functional role of leptin in the airway is not yet known. However, studies showing that leptin is involved in lung development and fibrotic responses suggest a role for leptin in airway remodeling (13-15). There are multiple other adipokines produced by adipose tissue including adiponectin. Shore *et al* have shown that adiponectin (which decreases in proportion to obesity) may ameliorate airway reactivity in an allergic mouse model of asthma (16). Tumor necrosis factor- α may also be involved: obese mice deficient in tumor necrosis factor receptor 2 have decreased airway reactivity compared to other obese mice (17). Adipose tissue elaborates a variety of other mediators such as interleukin 6, interleukin 8, and plasminogen activator inhibitor – 1, all of which could have direct and indirect effects on the airway. As we learn more about the function of these adipokines and their function in the airway, we will gain a better understanding of the pathogenesis of asthma in obesity.

Obesity produces profound changes in immune function, which have important implications not only for host defense, but also for immune diseases such as asthma (18). Obesity alters macrophage function in the lung (19, 20), and appears to have important effects on lymphocyte function (18, 21). We have shown that CD4 function, measured by response to polyclonal stimulation, appears to be increased after bariatric surgery (22, 23), while others have shown that mediastinal lymphocyte function is altered in mouse models of obese asthma (23). This suggests that alterations in lymphocyte and immune cell function are

likely to be important disease modifiers in the pathogenesis of allergic asthma. Alterations in lymphocyte function are not simply of relevance to the pathogenesis of disease, but altered immune cell function also alters response to therapy in asthma, as discussed below.

In summary, obesity has pleiotropic effects on mechanics, immune function, and mediators involved in airway function to produce asthma in obese subjects, and alter the response to standard medications in obese asthmatics.

Phenotypes of Asthma in Obesity

Asthma in obesity is not one uniform disease. There appear to be at least two phenotypes of asthma in obesity, which can be distinguished by age of onset and markers of T_H2 inflammation. Obese patients with early-onset asthma tend to have more atopic disease, higher immunoglobulin E, and greater bronchial hyperresponsiveness. These people appear to have allergic asthma that is complicated by obesity. In contrast, obese patients with late onset asthma tend to have less atopy, bronchial hyperresponsiveness and lower levels of T_H2 inflammation. These people have asthma that has developed in the setting of obesity (22, 24, 25). One size may not fit all when it comes to considering treatment of asthma in obesity.

Medications for the treatment of asthma in the obese

While there are multiple reasons that obese asthmatics suffer with poor asthma control, one significant reason appears to be that they have altered response to controller medication. There is now abundant evidence that the obese do not respond as well to standard controller therapy, as summarized in Table 1 (26-34). Inhaled corticosteroids and combination inhaled corticosteroid-long acting agonists appear to be superior to montelukast for the treatment of asthma in obese patients (28, 31, 32). Although response to controller therapy is altered, response to rescue therapy is not; Yeh *et al* reported that obese patients had similar improvements in peak flow in response to rescue albuterol therapy in the emergency department (35).

There are many reasons that the obese do not respond as well to these controller medications. They have altered cellular responses to steroids, with Sutherland *et al* showing a reduced induction of MKP1, a signaling molecule involved in steroid responses, with dexamethasone treatment of mononuclear cells isolated from patients (36, 37). The phenotype of asthma in obesity is different than that in lean asthmatics, and current therapies have been developed to target allergic asthma in lean individuals. It is not surprising that the obese do not respond as well to these medications. All currently approved asthma medications have been developed using lean animal models of asthma, and tested in patient populations that are far leaner than the typical patient population encountered today. Indeed, we are not aware of any published prospective studies that have investigated response to drug therapy specifically in obese asthmatics. For the moment treatment recommendations are the same in lean and obese asthmatics, future trials focusing on the development of treatments specifically for obese patients are much needed.

Weight Loss for Asthma in Obesity

If obesity is a risk factor for poorly controlled asthma, it is perhaps self-evident that weight loss should be considered as an intervention for obese asthmatics. However, the data to support this type of intervention are sparse. A number of uncontrolled studies have been published suggesting that bariatric surgery improves asthma control in obese asthmatics (22, 38, 39). However, bariatric surgery is a radical intervention associated with expense and complications, and so it is more practical to determine if life-style interventions could improve asthma control in obese patients. A recent Cochrane review found only 4

randomized controlled trials of weight loss in asthma, and only two of these had been published in more than abstract form (40). Stenius-Aarniala conducted a 12 week randomized controlled trial of weight loss, and found improvements in peak flow with weight loss (41). A more recent study by Scott *et al*, in which patients were randomized into one of three groups (exercise, diet plus exercise or diet alone), found that a 12 week intervention that produced weight loss produced a significant improvement in asthma control (42). The data in this latter study suggested that approximately 5 % weight loss was required to produce a significant improvement in asthma control as measured by a standardized questionnaire (43). As of yet, there are no multi-center studies published of weight loss for asthma.

Dietary Interventions for Asthma in Obesity

The obesity epidemic is not just associated with an excess of caloric intake relative to energy expenditure, but there has been a major shift in the type of diet consumed by individuals, particularly in developed countries. Diets are now higher in fat, salt and sugar, and lower in fiber and anti-oxidants. Synthetic trans-fats have moved into the food supply. Certainly this predisposes to weight gain and obesity, but this complex natural experiment with nutrients has a major effect on inflammation and airway biology. There is an emerging literature showing how this type of diet leads to increased production of inflammatory mediators and reactive oxidant species, which are highly relevant to asthma in obesity (44).

Even before the obesity epidemic there was a great deal of interest in the role of anti-oxidants and vitamins, such as carotenoids, selenium, zinc, magnesium, ascorbic acid and vitamin E, in the pathogenesis of asthma and as potential interventions for the treatment of asthma in normal weight populations. A large number of observational trials have been published on this subject. Interventional clinical studies have yielded conflicting results (45-49). One of the more interesting interventions particularly pertinent to obesity is vitamin D (50). Vitamin D is decreased in proportion to obesity, and has important effects on immune function. There are ongoing studies with vitamin D supplementation to determine if supplementation can improve asthma outcomes, and it will be of particular interest to understand the potential role of vitamin D in obese patients with asthma.

The quantity and composition of fats in the diet changes radically with a shift to a westernized diet, and this may be important in the pathogenesis of airway disease. A diet high in saturated fatty acids, and low in fiber has been associated with severe asthma, and a high fat diet (particularly a high trans-fat diet) can induce airway neutrophilia, even in normal weight asthmatics (51). There are a number of observational studies suggesting that certain types of fat may be involved in risk of developing asthma and airway responses in those with established asthma. Li *et al* found that a diet high in omega-3 polyunsaturated fatty acids, such as found in fish oil, was protective against the development of asthma in adult-hood (52), others have reported that supplementation with omega-3 polyunsaturated fatty acids reduces response to allergen challenge (53) and exercise induced bronchoconstriction (54). Recent publications suggest that nutritional formulas rich in these omega-3 polyunsaturated fatty acids have benefit on exhaled nitric oxide and airway reactivity in children with asthma (55). The balance of omega-3 (such as are found in fish oil) to omega-6 fatty acids (such as linoleic acid found in sunflower oil) is also thought to be important, with one study suggesting improvements in markers of inflammation in children receiving supplementation with omega-3 fatty acids, but not with omega-6 fatty acids, though this was not associated with clinical improvements in asthma (56).

There are also data on the effect of a Mediterranean diet in patients with asthma. One recent open label study of 38 patients found a trend towards improvement in asthma symptoms in

patients on a Mediterranean diet (57). An observational study of 1125 Greek school children found that adherence to a Mediterranean diet was associated with a lower likelihood of being diagnosed with asthma (58); however a Spanish observational study of 7000 schoolchildren did not find a protective effect of a Mediterranean diet against the development of asthma (59). Romieu *et al* found that a high fruit and vegetable intake, and adherence to a Mediterranean diet was associated with better lung function in a study of 158 asthmatic and 50 non-asthmatic children in Mexico (60). It is possible that unmeasured confounding factors may explain the different findings in these observational trials, and that different factors may be important in the development of asthma versus control of asthma in those with established disease.

Fruit and vegetable intake are also likely to be an important component of diet. Fruit and vegetables are high in anti-oxidants which may be beneficial for airway inflammation in asthma. Some recent studies suggest that high fruit and vegetable intake may be associated with a lower incidence of asthma (61, 62). Wood *et al* found in a study of 137 adult asthmatics supplemented with a high oxidant diet (with 2 fruits and 5 vegetable servings for 14 days, then placebo versus lycopene supplementation) that the low anti-oxidant group had a decrease in lung function, and that high anti-oxidant group had decreased exacerbations which was not seen in those supplemented with the anti-oxidant lycopene. This suggests that it was whole food supplementation that was important in the reduction of asthma exacerbations (63).

At this point in time, the largely observational literature suggests that it is reasonable to consider a low fat, high anti-oxidant diet and/or weight loss in an obese patient with poorly controlled asthma, with the caveat that there are obvious limitations to observational and non-randomized study designs which are frequently subject to confounding. There is a growing wealth of literature pertaining to cardiac disease, and the benefit of low fat diets, diets high in anti-oxidants and Mediterranean type diets on cardiovascular outcomes. Yet there are essentially no large multi-center studies investigating similar life-style and dietary interventions in asthma. Such studies are needed to manage the growing population of obese, poorly controlled asthmatics that is the reality of the 21st Century.

Exercise and Asthma

Exercise may be part of a lifestyle intervention to reduce weight in asthma, or could be considered as an intervention by itself. There are data in animal models to suggest that exercise can reduce allergic airway inflammation (42, 64-66), but only small studies of exercise in the treatment of human asthma. These small studies are likely underpowered to see significant differences in asthma outcomes (67). Scott *et al* investigated the role of exercise as part of a three-arm randomized trial in which obese asthmatics were randomized to dietary intervention, exercise, or exercise and dietary intervention for the treatment of asthma. Only the patients in the dietary intervention and exercise plus dietary intervention (both these groups achieved significant weight loss) experienced significant improvements in asthma control. The exercise group maintained a stable weight and did not experience a significant improvement in asthma control, but did have a significant decrease in airway eosinophilia (which is consistent with earlier findings from mouse models of allergic airway inflammation and asthma) (42).

There are currently no large studies of exercise as an intervention to improve asthma control in obesity, though preliminary data from small studies suggest it may be particularly helpful to treat obese asthmatics as part of a lifestyle intervention including weight loss.

Co-Morbidities and Asthma

Certain co-morbidities in obesity may contribute to both the pathogenesis of asthma in obesity, and disease activity. Gastro-esophageal reflux disease, and obstructive sleep apnea are two such co-morbidities.

GERD and Asthma

Gastro-esophageal reflux disease is increased in proportion to obesity, and there is some evidence to suggest that GERD may predispose towards the development of asthma based both on epidemiological data and animal models of acid reflux. Mechanistically, acid reflux may lead to airway pathology: instillation of acid in the esophagus may lead to vagally induced bronchospasm, and aspiration of acid contents directly into the airway could also lead to airway disease (68, 69). There have been a number of studies investigating the treatment of acid reflux in obesity. One study of poorly controlled asthmatics with minimal reflux symptoms found that treatment of acid reflux did not improve asthma control, even in those with pH probe positive reflux (70). In a post-hoc analysis, we found no relationship between any marker of acid reflux and asthma control in obese patients (71). This suggests that if a patient does not have symptomatic reflux, occult reflux is unlikely to be contributing to severe asthma in obesity.

Obstructive Sleep apnea and asthma

Obesity is a major risk factor for obstructive sleep apnea (OSA). With the ever increasing epidemic of obesity, OSA now affects about 9-24 % of men and about 4-9 % of women ages 30 – 60 years (72). There appears to be an important link between OSA and asthma, with a number of studies suggesting a high prevalence of OSA in asthma, and that OSA is associated with poorly controlled asthma (Table 2) (71, 73-77).

There is clear epidemiological data linking asthma and obstructive sleep apnea in obesity, and a number of potential pathophysiological mechanisms that may link these two conditions.

Obese individuals breathe at low lung volumes because of the mechanical loading effects of obesity on the respiratory system, as noted earlier. This means that functional residual capacity is close to residual volume, and so at end-exhalation many airways are close to closing volume and may actually close, and then reopen with inhalation. This repetitive opening and closing is exacerbated by the increased tidal volume following an apnea. In fact a study of seven patients with significant sleep apnea found total lung resistance and elastance increased during the apneic episodes and returning to baseline after an arousal, suggesting that changes in lung physiology do occur during apneic episodes (78). Not only does this induce acute changes in lung physiology during the apneic episode, but repetitive opening and closing may induce trauma and inflammation in the airway (79), and some studies have reported an association between markers of airway oxidative stress and other measures of airway inflammation in patients with OSA (80, 81). It is also possible that the repetitive Muller maneuver (inspiration against a closed glottis) that occurs in obstructive sleep apnea may cause inspiratory collapse of sections of the airways. Other potential factors that may narrow the airways in patients with obstructive sleep apnea include negative intrathoracic pressure producing edema of the airway wall, and narrowing of airway diameter, (82). Increased vagal tone, which is known to occur in sleep apnea, may aggravate bronchoconstriction (83). Thus there are numerous potential direct pathophysiological interactions between sleep apnea and asthma.

There are also indirect factors through which sleep apnea may lead to airway disease. Sleep apnea may indirectly affect asthma through effects on gastroesophageal reflux disease, as

apneic episodes increase negative intrathoracic pressure predisposing to aspiration. Reflux events are more frequent, and of longer duration in patients with OSA than controls, and treatment of OSA with CPAP reduces reflux (84, 85).

As noted above, there is evidence that sleep apnea contributes to increased symptoms and poor control in asthma, and there are a number of potential links between these two diseases. There are also a number of small studies suggest that treatment of sleep apnea improves symptoms and lung function in asthma (Table 3), though larger studies in more diverse patient populations are clearly required.

There may also be indirect benefits of CPAP therapy on asthma, independent of effects on sleep apnea. Xue *et al* have shown that CPAP therapy reduces airway reactivity in animal models of asthma (86), and mechanical loading of airway smooth muscle has effects on transcription of signalling molecules involved in regulation of protein expression in smooth muscle (87). A small study of CPAP for the treatment of asthma showed that CPAP therapy reduced airway reactivity (88), and a multi-center study of 12 weeks CPAP versus sham CPAP therapy is ongoing (clinicaltrials.gov number NCT01629823). This latter study excludes very obese participants, and participants with sleep apnea, in order to focus on the isolated effects of CPAP therapy on asthma, and not to confound the study with patients also suffering with sleep apnea. However, it would be appropriate for future studies to focus on obese patients with poorly controlled asthma, to determine if CPAP therapy might be an appropriate intervention for obese asthmatics, even independent of OSA.

Conclusions

Obesity is a major risk factor for asthma, and is changing the type of asthma routinely encountered in medical practice throughout the world. The pathogenesis of asthma is altered in obesity, and obese patients do not respond as well to standard controller therapy. Adjunctive therapies such as change in diet, weight loss and exercise, with consideration of treating sleep apnea, should prove useful in the treatment of these patients, though large trials of these types of interventions are currently lacking.

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Table 1

Recent publications reporting on differential response to therapy in obese asthmatics.

Author	Year	n	Population	Age	Main Finding
Peters Golden(31)	2006	3073	pooled clinical trial (Merck)	18 years	obese had fewer asthma control days on ICS, response to montelukast did not decrease with BMI
Boulet(27)	2007	1242	pooled clinical trial (GSK)	18-82	obese less likely to achieve control on ICS and ICS/LABA
Sutherland(33)	2009	1265	Pooled clinical trial (NHLBI Asthma Clinical Research Network)	adult	Obese had decreased response of eNO to ICS, decreased response of FEV1, FEV1/FVC and PC20 to ICS/LABA
Camargo, Boulet(28)	2010	1510	pooled clinical trial (GSK)	15 years	Obese have decreased response to ICS, with some improvement over time, ICS superior to montelukast
Camargo, Sutherland(29)	2010	475	post hoc analysis of clinical trial, African Americans only (GSK)	12-65	patients with BMI 40 had reduced response in pm Peak flow, and increased exacerbation rates
Sutherland, Camargo(32)	2010	1052	pooled clinical trial data (GSK)	15 years	Obese had reduced response to ICS, though ICS superior to montelukast
Forno(30)	2011	1207	Childhood Asthma Management Program	15 years	overweight and obese children less responsive to ICS in terms of lung function
Yeh(35)	2011	180	ED population	adults	obese and non-obese had similar response to albuterol and rates of admission
Anderson(26)	2012	72	post hoc analysis of single center clinical trial	18-65 years	Overweight and Obese had decreased response in terms of eNO and symptoms
Telenga(34)	2012	276	pooled data from single center studies	18-60 years	Obese had decreased FEV1 response to steroids (ICS and systemic pooled)

ICS: inhaled corticosteroid

LABA: long acting beta agonist

eNO: exhaled nitric oxide

GSK: GlaxoSmithKline

Table 2

Prevalence of OSA in patients with asthma

Study	Subjects	Methodology	Findings
Teodorescu 2012 (73)	452 patients with Asthma	Sleep disorders Questionnaire(SA-SDQ) and Juniper asthma control questionnaire	109/472(23%) met definition of high risk OSA. High risk OSA was linked with not well controlled asthma.
Dixon 2011 (71)	402 patients with asthma	Self- reported symptoms of sleep apnea	Worse asthma control associated with symptoms of sleep apnea.
Sharma 2011 (74)	29 asthmatics,85 healthy controls	Berlin questionnaire and PSG	High risk of OSA present in 62 % Asthmatics, 8% of controls($p<0.0001$)
Julien 2009 (75)	26 severe asthmatics, 26 moderate asthmatics and 26 healthy controls	Polysomnogram (Chicago criteria)	OSA found in 88% severe asthmatics, 58% moderate asthmatics, and in 31% controls.
Alharbi 2009 (76)	606 patients with OSA	Spirometry	213/606 patients with OSA had asthma (35.1%)
Auckley 2007 (77)	177 asthmatics 328 non asthmatics	Berlin Questionnaire	213/606 patients with OSA had asthma (35.1%)

Table 3

Effects of treatment of OSA in Asthma

Study	Subjects	Methodology	Findings
Chan 1987(32)	9 patients with nocturnal asthma and OSA	CPAP for sleep apnea	Nocturnal asthma control and PEFR improved
Lyn 1995 (33)	48 patients: 16 with OSA, 16 with snoring and 16 controls	Pre and post CPAP treatment Methacholine (MCT)challenge(only positive MCT patients received CPAP)	Reduced bronchial reactivity after CPAP
Lafond 2007 (34)	20 patients with asthma and OSA	Bronchial reactivity, spirometry and asthma QOL questionnaire	Asthma quality of life improved, but no change in FEV1 or bronchial reactivity.
Cifti 2005 (35)	43 patients with asthma	PSG and treated with CPAP	Asthma night-time symptom scores were improved significantly. Lung function did not improve