Obesity and Asthma: Impact on Severity, Asthma Control, and Response to Therapy

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Asthma is more prevalent in obese, compared with normal weight, subjects. Our aim has been to review current knowledge of the impact of obesity on asthma severity, asthma control, and response to therapy. Several studies have shown that overweight and obesity is associated with more severe asthma and impaired quality of life, compared with normal weight individuals. Furthermore, obesity is associated with poorer asthma control, as assessed by asthma control questionnaires, limitations in daily activities, breathlessness and wheezing, use of rescue medication, unscheduled doctor visits, emergency department visits, and hospitalizations for acute asthma. Studies of the impact of a high body mass index on response to asthma therapy have, however, revealed conflicting results. Most studies show that overweight and obesity is associated with less favorable response to asthma therapy, with regard to symptoms, level of FEV_1, fraction of exhaled nitric oxide, and airway responsiveness. Some studies suggest that asthma in the obese patient might be more responsive to leukotriene modifiers, orchestrated by leptin and/or adiponectin derived from adipose tissue, than to inhaled corticosteroids, possibly reflecting differences in the underlying airway inflammation in obese versus non-obese asthmatics. In conclusion, overweight and obesity is associated with poorer asthma control and, very importantly, overall poorer response to asthma therapy, compared with normal weight individuals. *Key words: asthma; obesity; asthma control; quality of life; response to therapy.* [Respir Care 2013;58(5):867–873.

Introduction

Overweight and obesity are associated with a number of well known health hazards, including diabetes and cardiovascular disease.[1] Furthermore, evidence from recent years suggests that obesity is also a risk factor for asthma.[2] According to the World Health Organization, the worldwide prevalence of obesity nearly doubled from 1980 to 2008,[3] and likewise a dramatic increase in the reported prevalence of asthma has been observed in recent decades.[4]

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Many prospective studies show that obesity is a risk factor for asthma and have found a positive correlation between increase in body mass index (BMI) and subsequent development of asthma. Obesity can reduce lung compliance and lung volumes and disturb the ventilation-perfusion relationship. Furthermore, obesity leads to higher levels of hormones produced in adipose tissue, of which some are pro-inflammatory. This systemic pro-inflammatory state might worsen the airway inflammation seen in asthmatic patients. The question is, therefore, what is the probable link between obesity and asthma? And not least, does obesity have an impact on the clinical manifestations of asthma, including response to therapy?

The aim of the present paper is to provide an overview of our current knowledge of the impact of obesity on the clinical manifestations of asthma, including asthma control and response to therapy.

Methods

A series of systematic searches were carried out, last updated October 2012, using the database PubMed. The strategy was intended to be broad, in order to maximize the capture of citations for peer-reviewed publications relevant to asthma and obesity. The PubMed searches were performed using the following algorithm of the National Library of Medicine's list of Medical Subject Headings (MeSH) terms: asthma, asthma control, asthma management, asthma severity or asthma-like symptoms AND obesity or overweight. The searches were repeated with these terms in combination with pathogenesis, therapy, and epidemiology. The citation pool was further supplemented from manual assessment of the reference lists accompanying other systematic reviews of aspects related to asthma in obese individuals and from other publications identified as being relevant for further review. The search was limited to English-language articles published after 1990, and only studies published in peer-reviewed journals were included in this systematic review. Studies published solely in abstract form were excluded because the methods and results could not be fully assessed.

Results

Obesity and Asthma Severity

In a retrospective review of medical records, Akerman et al[5] investigated the relationship between obesity and asthma in 143 adults (113 females), of whom 72% were obese, and reported a linear relationship between asthma severity, defined according to the National Heart Lung and Blood Institute guidelines, and BMI. Furthermore, females with asthma had significantly higher BMI, compared with males with asthma. Based on data from the National Asthma Survey in the United States, Taylor et al[6] studied the association between BMI and asthma severity in 3,095 adults with self-reported asthma. A total of 32% and 33%, respectively, of the sample were overweight and obese. Compared with non-overweight individuals, obese individuals with asthma were more likely to report persistent symptoms, more use of reliever medication, use of controller medication, and to be classified as having severe persistent asthma; the authors therefore concluded that obesity is associated with several characteristics of more severe asthma.

Varraso et al[7] studied in 2005 the relationship between BMI and asthma severity by sex. Information was gathered from 366 adults with well characterized asthma taking part in the Epidemiological Study on the Genetics and Environments of Asthma, a case control study to assess genetic and environmental risk factors and their interactions for asthma.[8] Severity of asthma was assessed by 3 criteria: clinical asthma severity score in previous year, hospitalization for asthma ever, and treatment with inhaled corticosteroids in previous year. The authors reported that an increase in asthma severity was significantly correlated with increasing BMI in women, but not in men. This association persisted after adjusting for confounders such as age, FEV_1 % predicted, smoking habits, BMI adjusted dyspnea, and the prevalence of asthma in first-degree relatives. Furthermore, the study also revealed that the association between BMI and asthma severity was strongest among women with early menarche. In line with these findings, Lavoie et al[9] reported that higher BMI is associated with higher Asthma Control Questionnaire (ACQ) scores and lower Asthma Quality of Life Questionnaire scores.[10]

In 2006, Mansell et al[11] investigated whether linkage between airway hyper-responsiveness and obesity could at least partly explain the prevalence of obesity in asthmatic adolescents. A total of 216 adolescents age 12–18 were divided into 3 groups: probands ($n = 55$) with one or more previous episodes of acute severe asthma; a control group ($n = 79$) with at least mild persistent asthma; and a group ($n = 82$) of healthy subjects. Mean values of BMI were found to be significantly higher among the 134 adolescents with asthma, compared with the group of healthy adolescents. Among the patients with asthma, 42% were found to be at risk of being overweight, and 25% to be overweight, compared with 29% and 16%, respectively, among the non-asthmatic controls. No relationship was found between total lung capacity and BMI or asthma status. Bronchial challenge testing with methacholine showed, as expected, airway hyper-responsiveness, defined as a PC_{20} (provocational concentration that produces a 20% decrease in FEV_1) of $\leq$ 10 mg/mL, more often in patients with asthma, compared to non-asthmatic subjects, but no significant association was observed between dy-

namic hyperinflation during positive challenges and overweight versus non-overweight status. Furthermore, no significant differences were observed between weight groups in overall asthma severity score, defined according to the Global Initiative for Asthma (GINA) guidelines,[12] or use of controller medication, whereas overweight subjects had greater decreases in inspiratory flows. The authors concluded that overweight in adolescents is associated with baseline air-flow limitation, but not airway responsiveness.

Peters et al[13] performed a 12-month randomized controlled trial comparing disease management with traditional care in 902 patients (473 children and 429 adults). The prevalence of overweight and obesity were 45% and 58%, respectively, among children and adults, and the relationship between BMI, asthma severity, spirometry findings, healthcare utilization and quality of life (QOL) was analyzed. The QOL was assessed using the pediatric and adult versions of the Asthma Quality of Life Questionnaire and the 36-item Medical Outcomes Study Short Form questionnaire. Information on all healthcare utilization was obtained by patient interviews and extensive medical record review. No association was observed between obesity and asthma severity, spirometry findings, QOL, or healthcare utilization in children, whereas in adult asthmatics obesity was associated with lower FVC and QOL, but not with asthma severity or healthcare utilization.

Obesity and Asthma Control

Lavoie et al[9] evaluated the associations between BMI and levels of asthma severity, asthma control, and asthma-related QOL in 382 adult out-patients with asthma, of whom 39% and 25%, respectively, were overweight and obese. Patients with higher BMI scored higher on the ACQ, independent of age, sex, and asthma severity defined by GINA guidelines.[12] There were significant associations between individual items on the ACQ, showing that patients with higher BMI had more early morning symptoms, greater limitation in daily activities, more shortness of breath and wheezing, and more need for rescue medication. Likewise, higher BMI was also associated with lower scores on the Asthma Quality of Life Questionnaire. Further analyses revealed that with increasing BMI the decline in asthma-related QOL, including activity limitations, was more pronounced in men, compared to women.

Peters-Golden et al[14] conducted a post hoc analysis assessing the possible influence of BMI on the response to asthma controller medication of data from a randomized controlled trial comprising 3,037 adults with moderate asthma, allocated to either montelukast, beclomethasone, or placebo. The primary end point in the analysis was asthma control days (defined as days with a maximum of 2 puffs of reliever medication, no night time awakening, and no asthma attacks). The analysis of data for patients on placebo revealed that normal-weight subjects had higher percentage of asthma control days (34%), compared with patients who were overweight (25%) or obese (26%).

In another study, also from 2006, Dixon et al[15] studied the effect of obesity on clinical presentation of asthma and response to therapy in a cohort of 488 (47% obese) subjects with mild to moderate persistent asthma. No difference was observed in cough, wheeze, or shortness of breath between the normal weight, overweight, and obese, whereas they found indications of poorer asthma control in the obese group, as assessed by ACQ score and use of rescue medication.

Saint-Pierre et al[16] carried out a longitudinal follow-up study of 406 out-patients with persistent asthma. Patient characteristics were described as a function of BMI < 25 kg/m^2 (260 patients, 160 women), BMI > 25 kg/m^2 (146 patients, 72 women), and as a function of asthma severity. Asthma control and severity were evaluated according to the GINA guidelines,[12] and asthma control was classified as acceptable or unacceptable. A clear relationship was found between BMI and severity, with more overweight patients in the severe asthma group. Furthermore, daily dose of oral corticosteroid and the total dose of corticosteroid during the previous year (< 2 g or > 2 g) were also positively correlated with BMI. The transition from unacceptable to acceptable asthma control was, after adjustment for covariates associated with BMI, less common in overweight patients. On the other hand, the reverse transition from acceptable to unacceptable asthma control state was not significantly associated with BMI.

In 2010 Kattan et al[17] studied the relationship between adiposity, sex, and asthma control in a group of 368 inner-city adolescents with asthma: 169 females, of whom 60% and 36%, respectively, had BMI $>$ 85th and 95th percentile of BMI for age, and 199 males, of whom 50% and 33%, respectively, had BMI $>$ 85th and 95th percentile of BMI for age. The analysis revealed that adiposity was related to poorer asthma control, as assessed by the Asthma Control Test in female subjects, but not in males.

Further studies by Rodrigo et al in 2007[18] and Taylor et al in 2008[6] found hospitalization rates to be higher among obese patients with asthma, compared to under/normal weight subjects with asthma. In keeping with this, Taylor et al[6] also found the rate of unscheduled doctor visits to be higher among obese individuals with asthma. A significant difference was also found between stay at the emergency department (2.3 h vs 1.9 h, respectively) and discharge rate after initial treatment at the emergency department (13.7% vs 6.8%, respectively) between overweight/obese and normal weight patients with asthma.

In a recent smaller study by Kilic et al,[19] the effect of obesity on asthma control was evaluated in 41 obese women

with asthma and 40 non-obese women with asthma, recruited from an out-patient clinic. Asthma was diagnosed according to the GINA guidelines,[12] and asthma severity was also classified according to GINA guidelines.[12] Data on serum leptin levels, fraction of exhaled nitric oxide, asthma control (assessed by the Asthma Control Test), and presence of atopy were obtained, and the relationship between these parameters and BMI were compared in the 2 groups. Uncontrolled asthma was found in 61% of the women in the obese group, compared to only 38% of those in the non-obese group, mean leptin level was significantly higher in obese patients with asthma, but no correlation was found between BMI and fraction of exhaled nitric oxide levels. The authors concluded that obesity is an important risk factor for uncontrolled asthma.

In a retrospective study, Quinto et al[20] studied the impact of overweight and obesity on asthma control. A cohort of 32,321 children, age 5–17 years, and treated with at least one asthma medication (controller or rescue) were enrolled. The study showed that overweight (BMI percentile for age 85–94%) and obese (BMI percentile for age $\geq$ 95%) children were more likely to have a higher amount of β agonists dispensed. Furthermore, overweight and obese children also had an increased risk of being prescribed rescue prednisolone (odds ratio of 1.21, 95% CI 1.13–1.29, and odds ratio of 1.28, 95% CI 1.21–1.36, respectively), compared with children with normal weight (BMI percentile for age 16–84%). The significant association between childhood obesity and worse asthma control and exacerbations persisted after adjusting for demographics, parental education level, asthma controller use, gastroesophageal reflux disease, and diabetes mellitus.

On the other hand, Clerisme-Beaty et al[21] performed a cross sectional assessment of asthma control in 292 patients with asthma. The majority were women (82%) and African-American (63%), recruited from primary care using 4 different validated survey tools: the Asthma Control and Communication Instrument, the Asthma Control Test, the ACQ, and the Asthma Therapy Assessment Questionnaire. A high prevalence of obesity (63%) was found, but regression analysis showed no association between obesity or increasing BMI level and asthma control, as assessed by the 4 questionnaires. These observations persisted after adjusting for confounders such as FEV_1, smoking status, ethnicity, sex, selected comorbid illness, and long-term use of asthma controller medication. Furthermore, no differences were found in asthma-related acute healthcare use or prescribed asthma medications by BMI categories.

In a study from Spain, Sastre et al[22] investigated the association between BMI and asthma control in a large sample of patients with asthma. Data were obtained from a previous study in which different ACQ domains (FEV_1, peak expiratory flow, and ACQ without lung function) and the Asthma Control Test were validated in a Spanish cohort comprising 607 adults with asthma (61% female), of whom more than 36% were found to be overweight or obese. No significant association was observed between BMI and asthma control, as defined by physicians or according to the Asthma Control Test or ACQ scores. The percentage of patients with poor asthma control was slightly higher in participants with both low BMI (BMI $<$ 18.5 kg/m^2) and obesity (BMI $>$ 30 kg/m^2).

For obvious reasons, the findings in the 2 latter studies led the authors to question the relation between obesity and asthma. However, the lack of association may be due to differences in measures of asthma control or characteristics of the studied cohorts, including proportion of obese individuals and females.

Obesity and Response to Asthma Therapy

Peters-Golden et al[14] conducted a study of 3,037 patients, evaluating the relationship between BMI and response to controller therapy with a leukotriene modifier (montelukast 10 mg qd nocte) and inhaled corticosteroid (beclomethasone 200 μg, 4 puffs bid) in patients classified as having moderate asthma. The end points were proportion of asthma control days (as defined above) and percentage change from baseline in FEV_1, night-time awakenings, and use of rescue medication. Their study showed that the efficacy of the 2 therapies by BMI category, as assessed by mean placebo-adjusted percentage of asthma control days, was significantly greater for beclomethasone than for montelukast in patients with normal BMI (18.6% vs 9.5%, respectively). However, this difference between treatment groups was statistically insignificant among overweight patients (18.8% vs 15.7%, respectively) and next to none among obese patients (13.9% vs 13.4%, respectively). The number of night-time awakenings was higher among overweight and obese patients, compared with normal weight participants, for both treatments. No statistically significant differences were found in use of rescue medication or percentage change in FEV_1 from baseline across the different BMI groups for any of the treatment groups. Based on their findings, the authors speculated whether asthma in the overweight and the obese may be a more leukotriene-driven type of asthma, compared with asthma in normal weight individuals, and, by that, whether controller medication including a leukotriene modifier could be beneficial for overweight and obese patients with asthma.

In keeping with this, Giouleka et al[23] conducted a relatively small study to determine whether obesity influences asthmatic airway inflammation, and whether the hormones leptin or/and adiponectin, produced in adipose tissue and regulating several metabolic and inflammatory pathways, contribute to a possible link between asthma-related and obesity-related inflammation. Their study comprised 100 patients with asthma and 60 healthy controls. Obesity

was found to be associated with increased urinary leukotriene levels, supporting the theory that alterations of leptin/adiponectin balance may be related to the presence of leukotriene inflammation in obese patients with asthma. Kilic et al[19] have also reported serum leptin levels to be significantly higher in obese patients with asthma, compared with non-obese patients with asthma.

Anderson and Lipworth[24] have recently studied the effect of BMI on response to inhaled budesonide in 72 patients with mild to moderate persistent asthma, divided into 2 groups: overweight (BMI $>$ 25 kg/m^2) and normal weight (BMI $<$ 25 kg/m^2). Each group received two 4-week treatment periods with inhaled budesonide 200 μg/d and 800 μg/d, and separated by a wash-out period. Outcome variables included FEV_1, fraction of exhaled nitric oxide, airway responsiveness (assessed as methacholine PC_{20}), total daily asthma symptom score, and overnight urinary cortisol/creatinine ratio. The study revealed that overweight patients with persistent asthma appear to have less symptoms and fraction of exhaled nitric oxide response to inhaled budesonide, whereas no differences were found in FEV_1 or airway responsiveness to methacholine between the overweight and normal weight group. In line with this, Sutherland et al[25] found elevated BMI to be associated with reduced in vitro response to dexamethasone in overweight and obese patients.

In a more recent study, Sutherland et al[26] explored whether increasing BMI influenced responses to treatment with inhaled fluticasone dipropionate and oral montelukast in patients with persistent asthma. A total of 1,052 subjects, divided into categories according to weight (underweight, normal weight, overweight, and obese), were enrolled in a double-blind, randomized, parallel-group trial of 12 weeks duration, comparing fluticasone and montelukast. This study showed, in contrast to the findings by Peters-Golden et al,[14] that fluticasone compared to montelukast leads to greater symptom reduction within all weight groups. They also found a statistically greater improvement in FEV_1 % predicted in all weight groups treated with fluticasone.

Furthermore, Camargo et al[27] studied the relationship between BMI and response to treatment with fluticasone propionate plus salmeterol (Diskus 100/50 μg) versus montelukast (10 mg) in a retrospective analysis of 4 previously published clinical trials. Enrolled patients were classified according to BMI as underweight ($<$ 20 kg/m^2), normal weight (20–25 kg/m^2), overweight (25–30 kg/m^2), obese 1 (30–35 kg/m^2), obese 2 (35–40 kg/m^2), and obese 3 ($\geq$ 40 kg/m^2). Outcome measures included FEV_1, asthma symptom score, and use of rescue albuterol. The study showed that, compared to subjects with normal BMI, the time to peak FEV_1 seems to be longer in the very obese patients, and that treatment responses to fluticasone/salmeterol were consistently greater, compared to montelukast, also at high BMI levels.

In an analysis of pooled data from 5 recently published studies, Boulet et al[28] studied the relationship between BMI and the response to fluticasone propionate, with (50/100 μg) or without (100 μg) the long-acting β_2-agonist salmeterol. A total of 1,242 individuals were included in the analysis, and asthma control was defined by the GINA guidelines.[12] The analyses showed that in both the obese and the non-obese groups of patients, the combination of fluticasone and salmeterol was more effective in terms of asthma control than fluticasone alone. The analysis also revealed that the likelihood of achieving well controlled asthma was significantly lower in obese subjects, particularly in individuals with a BMI $\geq$ 40 kg/m^2. The majority of patients with uncontrolled asthma had diurnal and/or nocturnal asthma symptoms and were also more likely to have daily use of rescue bronchodilators. Furthermore, obese patients also had an increase in daily symptoms over 24 hours, and an increase in bronchodilator reversibility.

Based on the Study of the Effectiveness of Low Dose Theophylline as Add-On Therapy in Poorly Controlled Asthma trial, Dixon et al[15] studied 488 patients with mild to moderate persistent asthma, all suboptimally controlled on their current therapy, as defined by a score $>$ 1.5 on the ACQ.[29] Patients were categorized according to BMI as normal-weight, overweight, and obese. The study showed an increased exacerbation rate in obese patients on theophylline, compared to those on placebo (8.1 vs 4.8 events per year), and the relative risk for an exacerbation associated with obesity among patients on theophylline (n = 150) was 3.7 (95% CI 2.2–6.3, $P < .001$). No significant difference in exacerbation rate was observed between non-obese and obese assigned to montelukast or placebo.

Discussion

Currently available published studies clearly show that obese patients with asthma have more severe asthma symptoms, poorer asthma control, and, furthermore, a less favorable response to asthma therapy, as assessed by symptoms. Furthermore, early morning symptoms, shortness of breath and wheezing, nighttime awakening, and limitation of daily activities are more prevalent and persistent in obese subjects suffering from asthma. Furthermore, greater use of rescue medication, primarily fast-acting β_2 agonist, has been observed among the overweight and obese individuals, compared with normal weight individuals with asthma. In line with this, and perhaps even more important, is the observation that obese individuals with asthma have a higher rate of hospitalization for acute asthma and unscheduled doctor visits, and lower QOL, as assessed by QOL questionnaires, compared with normal weight individuals with asthma.

Whether the above mentioned findings are direct consequences of asthma or a result of the mechanical stress that obesity puts on our respiratory system may be questioned. Some researchers have suggested that obesity leads to a pro-inflammatory state initiated by the cytokines produced in adipose-tissue, which in turn leads to asthma-like symptoms. If this is the case, the less favorable effect of asthma control might be due to the fact that the targeting of asthma control is wrong. In line with this, studies have revealed a poorer response to inhaled corticosteroids in obese asthmatics, which may be caused by differences in the mechanisms leading to asthma symptoms and clinical signs of asthma in obese and non-obese individuals, including the type of airway inflammation. Hopefully, future studies will provide us with further knowledge with regard to the complex interaction between obesity and asthma, and by that possibly define a distinct obese asthma phenotype. A clearly defined obese asthma phenotype may lead us to measures to improve the overall health of overweight or obese individuals presenting with asthma symptoms, not least by targeted pharmacologic therapy. The clinical consequence of this may be that asthma in the years to come should be managed differently in obese and non-obese individuals.

In our review of studies we noted the difference in results between sexes in a few studies. Varraso et al[7] reported that an increase in asthma severity was significantly correlated with increasing BMI in women but not in men. Lavoie et al[9] found increasing BMI to have a negative effect on asthma related QOL and activity limitations among men but not among women. Kattan et al[17] found obesity to be related to poorer asthma control in females but not in men. Given these conflicting observations, valid conclusions may not be drawn at present with regard to the effect of the sex-obesity interaction on asthma control, and further studies addressing this issue are clearly needed.

A number of studies have shown that overweight and obese individuals with asthma have significant improvements in asthma control, as assessed by symptoms, use of medication, level of lung function, and hospitalizations for asthma, after weight loss. The combination of poorer asthma control and response to therapy in overweight and obese individuals with asthma, and improvements in asthma control following weight loss, should teach all of us, not only healthcare providers, but also healthcare policy makers, that prevention of overweight and obesity is of utmost importance, both at the individual level and with regard to use of healthcare resources.

Conclusions

In conclusion, obesity has substantial negative impact on most clinically relevant measures of asthma control and response to therapy, and although the complex interaction between obesity and asthma is only partly understood, these findings clearly indicate that measures aimed at preventing overweight and obesity are likely to have substantial on overall asthma morbidity.

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