



Asthma and obesity: is weight reduction the key to achieve asthma control?

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Purpose of review

Obesity has significant negative impact on asthma control and risk of exacerbations. The purpose of this review is to discuss recent studies evaluating the effects of weight reduction on asthma control in obese adults.

Recent findings

Clinical studies have shown that weight reduction in obese patients is associated with improvements in symptoms, use of controller medication, and asthma-related quality of life together with a reduction in the risk for severe exacerbations. Furthermore, several studies have also revealed improvements in lung function and airway responsiveness, and more recently it has been shown that weight reduction following bariatric surgery has positive impact on small airway function, systemic inflammation and bronchial inflammation in this group of patients, which may explain the observed improvements in symptom control and lung function.

Summary

Weight reduction in obese adults with asthma leads to an overall improvement in asthma control, including airway hyperresponsiveness and inflammation. Weight reduction should be a cornerstone in the management of obese patients with asthma.

Keywords

asthma, asthma control, obesity, weight reduction

INTRODUCTION

The association between obesity and asthma has been well described, although the mechanisms underlying this association are incompletely understood [1]. Although obesity is associated with increased asthma incidence, prevalence, and severity [2,3], study findings have yielded conflicting data with regard to the relationship between obesity and asthma control [2,4]. In a cohort study comprising more than 25 000 children and adults, Schatz *et al.* [5] have shown that higher BMI increased the risk for asthma exacerbations, especially for autumn–winter exacerbations in adults, compared with their lean counterparts. In a further analysis of data from the same cohort, obesity at baseline was associated with subsequent poor asthma control, including exacerbations and high number of dispensed canisters of short-acting beta2-agonists [6].

According to the Global Initiative for Asthma guidelines, asthma is more difficult to control in obese patients, which may be because of differences in type of inflammation, contributory comorbidities,

such as sleep apnoea, diabetes, and gastroesophageal reflux disease, mechanical factors, probably together with other yet undefined factors [7]. In one of the largest analyses of the association between BMI and treatment response to asthma controller therapy comprising 3037 adults pooled from four randomized clinical trials, Peters-Golden *et al.* [8] observed an inverse association between the efficacy of inhaled corticosteroids and increasing BMI, assessed as number of asthma control days, whereas this association was not observed for patients treated with oral montelukast. In another post hoc analysis of pooled data from clinical trials, Sutherland *et al.* [9] reported, in contrast to the study by Peters-Golden *et al.* [8], that fluticasone dipropionate was superior to

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KEY POINTS

- Obese patients with asthma suffer from more severe asthma, including poor symptom control and high risk of exacerbations, and are less responsive to standard asthma therapy compared with other patients with asthma.
- Weight reduction, whether surgical or nonsurgical, improves asthma control, including asthma-related quality of life, and lung function.
- Weight reduction in obese patients with asthma reduces substantially the risk of severe asthma-related events, including emergency rooms visits and hospital admissions.
- Weight reduction in obese patients with asthma is associated with improvements in airway hyperresponsiveness and inflammation.
- Weight reduction should be a cornerstone in the management of obese patients with asthma.

montelukast in terms of improvement of forced expiratory volume in 1 second (FEV₁), use of rescue medication and symptom score across all BMI groups, which is in keeping with a study by Camargo *et al.* [10]. Furthermore, previous studies have also shown that obese patients with asthma, compared with normal weight patients with asthma, have more neutrophils in sputum, less improvement in lung function, and possibly also less reduction in sputum eosinophils following treatment [11–13]. Although the majority of available studies are posthoc analyses and some findings are conflicting, they reveal a picture of an altered, and in general less favourable, response to both reliever and controller medication in obese patients compared with patients with normal weight.

So, in contrast to normal weight patients, obese patients with asthma have poor asthma control, are at high risk of exacerbation, and, at the same time, have a poor response to standard asthma therapy. In light of the ongoing worldwide obesity epidemic (Fig. 1), we are forced to face the challenge, including finding new ways, of achieving best possible control in our obese patients with asthma.

The purpose of this review is to discuss recent studies addressing the impact of weight reduction on asthma control in obese adults.

DETERMINANTS OF SUCCESSFUL WEIGHT REDUCTION

The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens study revealed

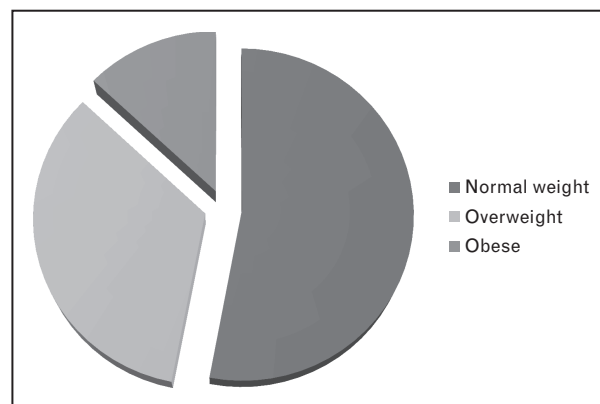


FIGURE 1. Adult Danish population 2013 divided according to BMI. Reproduced from Danish National Board of Health.

that more than 50% of adults with poorly controlled asthma in the United States are obese [14]. Therefore, it is of outmost importance to implement effective interventions that can lead to weight reduction in these patients. Unfortunately, achieving weight reduction is, in general, challenging and labour intensive, and has so far received little attention as part of the management of patients with asthma. Furthermore, there is very limited evidence to guide us on weight reduction interventions in patients with asthma.

To identify patient characteristics that predict weight reduction in adults with asthma, Scott *et al.* [15] investigated the association between baseline and change in asthma characteristics and eating behaviour and weight and fat reduction in 38 overweight and obese adults with asthma. Patients were randomized to dietary, exercise, or combined interventions targeting weight reduction over a 10-week period. Greater % weight reduction and % fat loss were associated with poorer asthma-related quality of life and lower FEV₁/forced vital capacity (FVC) ratio at baseline. Furthermore, male sex was associated with greater weight reduction, whereas a reduction in emotional eating was associated with greater weight reduction in women. The authors concluded that patients with more severe asthma may be more motivated for weight reduction, a motivational tool that might be useful in the clinical setting, possibly together with gender-tailored weight reduction programmes. The study provides very important insights into factors that predict weight reduction in obese adults with asthma. Not only will these findings be useful in the clinical management of asthma, but can also guide future trials of weight reduction in asthma patients.

WEIGHT REDUCTION, ASTHMA CONTROL, AND RISK OF EXACERBATIONS

In a randomized, open-label study of 33 adults (22 in the intervention group and 11 controls) with severe uncontrolled asthma and obesity (mean BMI 38 kg/m²), Dias-Júnior *et al.* [16] showed that the weight reduction programme (mean weight reduction 7.9 kg) was associated with an improvement in asthma control, assessed by the Asthma Control Questionnaire, after 6 months. In line with this, Scott *et al.* [17] have previously reported that a 5–10% weight reduction in obese patients with asthma has positive impact on several measures of asthma control.

Hasegawa *et al.* [18^{***}] more recently investigated the effect of bariatric surgery on risk for severe asthma exacerbations. A total of 2261 obese adults with asthma undergoing bariatric surgery were included in the self-controlled case series study. The combined incidence of pre and postsurgery emergency department visits and hospital admissions for asthma was the outcome of interest. The study revealed significantly fewer emergency department visits and hospital admissions (22 and 11%, respectively) in the 12-month period after bariatric surgery compared with the presurgery period. Furthermore, in the subsequent 13–24 months after bariatric surgery, the risk remained at this lower level. Not only does this study show that bariatric surgery decreased by half the risk of severe asthma exacerbations, it also clearly suggests that weight reduction is a way forward to achieve a reduction in asthma morbidity.

WEIGHT REDUCTION AND LUNG FUNCTION

Al-Alwan *et al.* [19] investigated potential differences in response to weight reduction in obese patients with ($n=10$) and without asthma ($n=13$). Lung function was measured, by conventional clinical tests and impulse oscillometry, before and 12 months after bariatric surgery. At the time of follow-up, control subjects had improvements in FEV₁, FVC, functional residual capacity, and total lung capacity, whereas patients with asthma only had an improvement in FEV₁. Furthermore, the two groups also had significantly different changes in respiratory system resistance, suggesting that the lung periphery is more collapsed by obesity in patients with asthma compared with nonasthmatic controls. The authors interpreted their findings as suggesting that asthma in obesity is related to an abnormality in the lung periphery. However, to establish the pathophysiology of the disease in obese patients with late-onset, nonallergic asthma

larger studies are clearly needed, with inclusion of men and, if possible, patients who become nonobese.

Improvements in lung function, including FEV₁ and FVC, following weight reduction in obese patients with asthma have also been reported from other studies [16,20–22].

WEIGHT REDUCTION AND AIRWAY RESPONSIVENESS

In a small study, Chapman *et al.* [23] compared changes from baseline in metacholine responsiveness in obese patients with early-onset asthma and high-serum IgE (T_H2-high) ($n=8$) and late-onset asthma and low-serum IgE (T_H2-low) ($n=5$) 12 months after bariatric surgery. The observations in the study highlighted the complex interplay between IgE status and asthma pathophysiology in obese patients, but showed an improvement in airway responsiveness in the T_H2-low obese patients. This may be important, as the late-onset phenotype is likely to be more prevalent among obese patients with asthma.

In a small, prospective, parallel-group study, Pakhale *et al.* [21] investigated 22 obese patients with asthma and airway hyperresponsiveness to metacholine. Of the enrolled patients, 16 followed a behavioural weight reduction programme for 3 months, and six (all waiting for bariatric surgery) served as controls. The primary outcome was change from baseline in airway hyperresponsiveness at 3 months; and the mean weight reduction in the intervention group was 16.5 kg compared with a mean weight gain of 0.6 kg in the control group. A significant improvement in airway hyperresponsiveness was found in the intervention group, whereas no change was seen in the control group. The study shows that weight reduction can improve overall asthma control and supports the importance of actively pursuing healthy weight reduction measures in this group of patients. However, the nonrandomized design and small number of patients are important limitations, but on the other hand it should be noted that patients were only included if the diagnosis of asthma was confirmed by a positive metacholine challenge test.

A decrease in airway responsiveness to methacholine after weight reduction in obese patients with asthma has also been reported by Al-Alwan *et al.* [19], van Huisstede *et al.* [24^{***}], and Dixon *et al.* [25], whereas Dias-Júnior *et al.* [16] found no changes in methacholine responsiveness.

Arismendi *et al.* [26] studied airway hyperresponsiveness to mannitol before and after bariatric surgery in 58 severely obese patients without a

history of asthma. Before bariatric surgery, airway hyperresponsiveness to mannitol was found in 28% ($n=16$) of the patients, compared with only 7% at follow-up 12 months after surgery. Furthermore, their study also revealed that weight reduction was the key factor associated with improvement in airway responsiveness. However, it should be noted that 15 of the 16 patients had lost their presurgery hyperresponsiveness at follow-up, whereas three presurgery nonresponsive patients became hyperresponsive to mannitol. Larger studies are, therefore, necessary to establish prevalence and characteristics of airway hyperresponsiveness before and after weight reduction in nonasthmatic obese adults.

WEIGHT REDUCTION AND AIRWAY INFLAMMATION

Van Huisstede *et al.* [24²²] studies whether the improvement in asthma control and lung function after weight reduction is because of improvements in mechanical properties of the airways or a reduction in systemic and airway inflammation. In a 12-month longitudinal study, lung function, asthma control, cellular infiltrates in bronchial biopsies, and markers of systemic inflammation were studied in obese patients with ($n=27$) and without ($n=39$) asthma undergoing bariatric surgery compared with obese patients with asthma but no surgical intervention ($n=12$). At the 12-month follow-up, an improvement in markers of systemic inflammation, including high-sensitivity C-reactive protein, adiponectin, and leptin, were observed in both groups having surgical intervention, whereas a decrease in mast cell numbers in bronchial biopsies was only seen in the group of patients having bariatric surgery. This first study to evaluate bronchial biopsies in obese patients with asthma before and after bariatric surgery, therefore, showed that weight reduction following surgery improves signs of systemic and airway inflammation. However, it should be noted that no change was observed in several other markers of both systemic inflammation, including $\text{TNF}\alpha$, and airway inflammation, including submucosal cell counts of eosinophils and neutrophils.

In a 12-month prospective study of asthmatic ($n=23$) and nonasthmatic ($n=21$) patients undergoing bariatric surgery, Dixon *et al.* [25] investigated the effect of weight reduction on airway hyperresponsiveness and markers of asthmatic airway inflammation. Apart from the above mentioned improvement in airway responsiveness to methacholine in asthmatics with normal serum IgE levels, the 12-month follow-up after surgery also showed a

Table 1. Effects of weight reduction in obese adults with asthma

Weight reduction in obese adults with asthma has positive impact on:

Asthma control (Asthma Control Questionnaire)

Symptoms

Lung function

Airway hyperresponsiveness

Airway inflammation

Emergency department visits for asthma

Hospital admissions for asthma

significant increase in proportion of lymphocytes in bronchoalveolar lavage fluid and the production of cytokines from activated peripheral blood CD4^+ T cells. These findings, therefore, support the notion that obesity produces a unique phenotype of asthma. On the other hand, in the study by Dias-Júnior *et al.* [16], no changes were reported in markers of airway inflammation.

Further studies are clearly needed to disentangle the highly complex interaction between airway inflammation and obesity.

CONCLUSION

Weight reduction in obese patients with asthma leads to an improvement in symptoms, lung function, medication requirements, and efficacy of pharmacological therapy together with a reduction in airway inflammation and hospital admission rate, and by that an improvement in overall asthma control. Weight reduction, surgical or nonsurgical, should be a cornerstone of the future management of asthma in obese patients (Table 1).

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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