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Asthma symptoms in obese adults: The challenge of achieving asthma control

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The association between asthma and obesity is well-described, but not straightforward, and according to current guidelines asthma control is more difficult to achieve in obese patients. The currently available studies evaluating response to pharmacological asthma therapy in obese patients show that these patients have an altered, in general less favorable, response to both reliever and controller medication compared to normal weight patients. However, at present, the limited available evidence precludes evidence-based recommendations. The 'obesity-related asthma' phenotype has different characteristics, including association with atopy and type of airway inflammation, compared to 'classic' asthma. Furthermore, weight loss in patients with this phenotype leads to an improvement in symptoms, lung function, and airway responsiveness, as well as a reduction in medication utilization and hospital admissions. Obese patients, who present with symptoms suggesting a diagnosis of asthma, may have a distinct phenotype or a disease mimicking asthma, likely to have a potentially higher remission rate. And by that, our approach to this group of patients should combine pharmacologic and non-pharmacologic therapies, including exercise, weight loss and dietary interventions, instead of primarily focusing on disease control by stepping up asthma therapy.

The association between obesity and asthma is well-described, although the mechanisms underlying the association are incompletely understood [1]. According to the Global Initiative for Asthma guidelines, asthma is more difficult to control in obese patients, possibly due to a different type of inflammation, contributory co-morbidities such as sleep apnea and gastroesophageal reflux disease, mechanical factors, as well as other yet undefined factors [2]. However, since we are witnessing an ongoing obesity epidemic, we are forced to meet the challenge of achieving best possible disease control also in our adult patients with asthma symptoms and concomitant obesity.

Response to asthma therapy in the obese adult

In a *post hoc* analysis of data from four randomized trials comprising 3,037 adults with moderate to severe asthma, Peters-Golden *et al.* [3] evaluated the

association between treatment response and BMI. All enrolled patients had bronchodilator reversibility at enrolment, and were randomized to treatment with inhaled corticosteroid (ICS), montelukast or placebo. The authors reported that the efficacy of ICS was inversely associated with increasing BMI, as measured by the number of asthma control days, whereas this correlation was not observed in the group treated with montelukast. Compared to ICS, the authors concluded that obese patients with asthma had a better response to montelukast [3].

Anderson and Lipworth [4] also performed a *post hoc* analysis of 72 asthma patients, classified as either overweight (BMI ≥ 25 kg/m²) or normal weight (BMI < 25 kg/m²), to study the association between BMI and response to increasing doses of ICS. All enrolled patients received two 4-week treatment periods with inhaled budesonide 200 and 800 μ g/day separated by a wash-out period. The analysis revealed that normal

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weight patients with asthma had significantly greater improvements in asthma symptoms and fraction of exhaled nitric oxide with increasing ICS doses compared to the overweight patients with asthma, whereas no difference was found between the groups with regard to forced expiratory volume in 1 (FEV₁) and airway responsiveness to methacholine [4]. Furthermore, Sutherland *et al.* [5] also published a *post hoc* analysis of pooled data from two randomized controlled trials comprising 1052 patients with asthma, comparing the effect of 12-week treatment with oral montelukast (10 mg daily) and inhaled fluticasone dipropionate (88 µg twice a day). The participants were divided into four subgroups according to their BMI, that is underweight (BMI < 20 kg/m²), normal weight (BMI 20–24.9 kg/m²), overweight (BMI 25–29.9 kg/m²) and obese (BMI ≥ 30 kg/m²). In contrast to the study by Peters-Golden *et al.* [3], the authors reported that the efficacy of fluticasone dipropionate was superior to montelukast, as assessed by FEV₁, morning peak flow, use of rescue bronchodilator and symptom scores in all BMI groups [5]. In keeping with this, Camargo *et al.* [6] reported a greater effect of 12-week treatment with fluticasone plus salmeterol (100/50 µg twice daily) versus montelukast (10 mg daily) across BMI group based on a retrospective analysis of four previously published clinical trials, where efficacy was assessed by FEV₁, asthma symptom score and use of rescue bronchodilator.

In a retrospective study of pooled data from four clinical asthma trials, Telenga *et al.* [7] showed that obese patients had more neutrophils in both sputum and blood and less improvement from baseline in FEV₁ (50 vs 220 ml, respectively) compared to their lean counterparts, whereas no overall difference in asthma severity was reported. Furthermore, obese patients with asthma had less reduction in sputum eosinophils. These findings, therefore, suggest a less favorable effect on airway inflammation of ICS in obese patients with asthma. In contrast to the study by Telenga *et al.* [7], an association between obesity and eosinophilic airway inflammation has not been reported from previous studies [8–10].

In a *post hoc* analysis, Boulet *et al.* [11] studied the relationship between body mass index and the response to fluticasone propionate (ICS) twice a day, with (50/100 µg) or without (100 µg) the long-acting β₂-agonist salmeterol. A total of 1242 individuals were included in the analysis, and asthma control was defined according to Global Initiative for Asthma [2]. In both obese and non-obese patients, the combination of fluticasone and salmeterol was more effective in terms of asthma control than fluticasone alone. However, the authors also reported that the likelihood of achieving well-controlled asthma was significantly lower in obese subjects, particularly in individuals with a BMI ≥ 40. In contrast to a recent study by McGarry *et al.* [12], obese patients had more pronounced bronchodilator reversibility.

Based on data from the Study of the Effectiveness of Low Dose Theophylline as Add-On therapy in Poorly Controlled Asthma trial, Dixon *et al.* [13] analyzed data for 488 patients with mild to moderate asthma, all sub-optimally controlled on their current therapy as defined by an Asthma Control

Questionnaire score >1.5 [14]. 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 < 0.001).

The studies reviewed above provide us with important observations in response to both reliever and controller medication in obese patients with asthma. However, the majority of reported observations are based on post hoc or retrospective analyses, and is by that primarily hypothesis generating. There is, therefore, an urgent need for well-designed clinical trials addressing the effect of therapy, including new treatment options, in obese patients with asthma diagnosed by objective criteria.

Effect of weight reduction on asthma control

The majority of studies investigating the effects of non-surgical and surgical weight reduction in overweight and obese adults with asthma have shown positive effects on several measures of disease control [15,16]. However, it should be recognized that the studies are very different in terms of enrolled patients, interventions and outcomes examined [15,16].

Very recently, van Huisstede *et al.* [17] reported findings from a longitudinal study of obese patients with asthma undergoing (n = 27) or not undergoing (n = 12) bariatric surgery compared with non-asthmatic subjects (n = 39) undergoing bariatric surgery. Lung function, asthma control, cellular infiltrates in bronchial biopsies and circulating markers of systemic inflammation were measured at 3, 6 and 12 months. Bariatric surgery had positive effects on small airway function, systemic inflammation and number of mast cells in the airways, which may explain the effect of weight reduction on asthma control, medication use, quality of life and lung function.

In line with this, Boulet *et al.* [18] have previously published a 12-month prospective controlled trial of patients with doctor-diagnosed asthma, where 12 obese patients (mean BMI 51 kg/m²) undergoing bariatric surgery were compared with 11 obese patients (mean BMI 46 kg/m²) not undergoing surgery. Six months after surgery, patients in the intervention group (mean BMI 38 kg/m²) had significant improvements in symptoms, lung function, use of asthma medication and airway responsiveness.

In a randomized trial of 46 overweight and obese (mean BMI 34 kg/m²) adults with physician-diagnosed asthma, Scott *et al.* [19] allocated patients to either a calorie restricted diet, physical activity or a combination of both interventions for 10 weeks. No differences in baseline characteristics, including asthma status and asthma medications, were found between the groups. This study showed that even a modest weight reduction (5–10% of pre-intervention body weight) leads to an improvement in asthma control (assessed by the asthma control questionnaire score), lung function and quality of life. Furthermore, a significant reduction in sputum eosinophils was seen in patients allocated to the exercise intervention.

In keeping with the studies reviewed above, the first clinical randomized study by Stenius-Arniala *et al.* [20] showed improvements in symptoms, health status and lung function in 38 obese patients with doctor-diagnosed asthma compared to a matched control group. Over an 8-week period, patients in the intervention group, that is, supervised weight reduction program (low energy diet), lost 14.5% of their baseline body weight, compared to 0.3% in the control group.

The available studies document that weight reduction in obese patients leads to substantial improvements in symptoms, quality of life, asthma control, including objective measures of disease activity, and probably not least with regard to the risk of exacerbations [21]. Our current knowledge, therefore, supports the importance of facilitating weight reduction in overweight and obese adults with asthma.

Management of asthma symptoms in obese adults

Obese patients with asthma have, as reviewed above, an altered response to asthma therapy, including controller medication [22]. In general, obese patients with asthma symptoms seem to be less responsive to asthma medication than non-obese patients with asthma [23]. However, at present, conflicting findings preclude evidence-based recommendations for pharmacological management of asthma symptoms in obese adults.

On the other hand, the 'obesity-related asthma' phenotype is characterized by altered lung volumes, increased work of breathing, no association with atopic status, increased systemic inflammation and less eosinophil airway inflammation, and a much weaker association between clinical expression of asthma

and level of airway responsiveness [24]. Furthermore, weight loss in obese patients with asthma symptoms results in an improvement in respiratory symptoms, medication needs, lung function, airway responsiveness and markers of airway inflammation [16,18]. Asthma-like symptoms in the obese adult may, therefore, represent a subtype of asthma or even a different disease than asthma, which makes it of outmost importance always to diagnose asthma in an obese patient by objective measures of airway function. In line with this, assessment of disease control and effect of pharmacological therapy should be examined carefully.

In conclusion, asthma symptoms in obese adults are likely to represent a distinct disease entity or even another disease than asthma based on response to pharmacological therapy and effect of weight reduction. Instead of attempts to achieve best possible disease control by pharmacological asthma therapy alone, more focus should be on tailoring the management strategy to the individual patient, as weight reduction is likely to be at least as important as pharmacological therapy in obese adults with asthma symptoms.

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