

REVIEW

Asthma and obesity

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Summary

The prevalence and incidence of asthma have increased among obese children and adults, particularly among women. Obesity seems to be a predisposing factor for the development of asthma, but the underlying mechanisms of its influence are still uncertain. Various hypotheses have been proposed to explain the link between obesity and asthma such as a common genetic predisposition, developmental changes, altered lung mechanics, the presence of a systemic inflammatory process, and an increased prevalence of associated comorbid conditions. Over-diagnosis of asthma does not seem to be more frequent in obese compared to non-obese subjects, but the added effects of obesity on respiratory symptoms can affect asthma control assessment. Obesity can make asthma more difficult to control and is associated with a reduced beneficial effect of asthma medications. This could be due to a change in asthma phenotype, particularly evidenced as a less eosinophilic type of airway inflammation combined to the added effects of changes in lung mechanics. Weight loss is associated with a universal improvement of asthma and should be part of asthma management in the obese patient. Additional research should be conducted to better determine how obesity influences the development and clinical expression of asthma, establish the optimal management of asthma in this population and determine how obesity affects long-term asthma outcomes in these patients.

Keywords airway hyperresponsiveness, airway inflammation, asthma, asthma control, body mass index, expiratory flows, obesity, perception, respiratory symptoms

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Epidemiological links between asthma and obesity

Introduction

Obesity is an increasing worldwide problem that has taken epidemic proportions [1]. The World Health Organisation (WHO) considers that by 2015, more than 700 million individuals over 14 years of age will be obese [2]. Weight gain is associated with an increased prevalence of many chronic conditions including diabetes, hypertension, and respiratory problems such as obstructive sleep apnoea (OSA) [3]. Over the course of the last two decades, asthma has been added to the list of conditions whose development or clinical features can be influenced by obesity [4–6].

Prevalence of asthma in obese subjects

An increased prevalence of asthma has been reported in both underweight and obese subjects (body mass index

(BMI) > 30 kg/m²) [7–9]. As reported by Ford, most cross-sectional studies in adults with asthma show an increased prevalence of obese subjects when compared to normal population suggesting that obesity could increase the risk of asthma [10]. Furthermore, such a relationship between asthma and obesity has been consistently found regardless of the ethnic origin of the population studied [7, 10–14].

Among children and adolescents, this link between asthma and obesity is also present, but not as consistently [10]. In a cross-sectional study, Cottrell and colleagues reported that there was an association between obesity and asthma in a large sample of US children, asthma prevalence increasing with BMI percentile [15]. However, the aforementioned study, like several others, presented some methodological weaknesses such as asthma diagnosis based solely on parental reporting [16]. Nevertheless, prospective analyses of school-aged cohorts also show that asthma prevalence and incidence are increased by the presence of obesity [17, 18]. Such

association seems to be recent and predominates mostly among children from a lower socioeconomic position [19, 20].

Asthma incidence

The majority of studies examining the risk of obesity-related incident asthma have found a significant positive association between BMI and a new diagnosis of asthma, although with variable risk ratios [5, 13, 21–25]. In a meta-analysis of adult prospective studies, Beuther et al. reported pooled odds of 1-year incident asthma in overweight and obese adults, respectively, of 1.51 and 1.92, with a dose-response effect of BMI on incident asthma.

Influence of gender on the relationship between asthma and obesity

Obesity is generally found to be more consistently associated with asthma in women than men [5, 13, 14, 21, 24, 26]. This does not seem explained by a diagnostic bias and selected population, but suggests a possible influence of sex hormones on this relationship. However, in an analysis of data from 4589 women and 4654 men taking part to the NHANES survey, followed over a decade [25], compared with normal weight participants, the odds ratio for subjects with a BMI over 35 kg/m² was 1.87 (95% confidence interval (CI) 1.12–3.13) and this was similar for men and women.

Similar observations were made in children, the association between asthma and obesity being stronger in girls than in boys [27]. In a study of 9828 children 6–14 years of age from American cities, an increased risk of a new asthma diagnosis in girls was associated with a higher BMI at entry into the study ($P = 0.009$) and greater BMI increase at follow-up ($P = 0.0003$), although extremes of annual BMI growth rates increased the risk of asthma in both boys and girls [18]. Finally, contrary to the previous studies, in a follow-up of 3792 children 7–18 years of age, the risk of asthma development from 1993 to 1998 was increased among overweight and obese boys, but not among girls [17].

Can over-diagnosis of asthma explain the changes observed in the obese?

In a study examining the possibility of over-diagnosing asthma among the obese, Aaron et al. showed that in both obese and non-obese patients, close to a third of patients with a physician's diagnosis of asthma had no evidence of asthma [28]. In a subsequent analysis, Pakhale et al. reported that older subjects, men, and

subjects with higher forced expiratory volume in 1 s (FEV₁) were more likely to have received a misdiagnosis of asthma [29]. Obesity was not an independent predictor of misdiagnosis, but for those with emergency visits in the past 12 months, the odds ratio for receiving a misdiagnosis of asthma for obese individuals as compared with normal weight individuals was 4.08 (95% CI, 1.23–13.5).

Effect of obesity on AHR

An increase in airway responsiveness (AHR) is a universal physiological feature of asthma. Discrepancies have been observed between the prevalence of self-reported or physician-made diagnosis of asthma and AHR. In many studies, no association was found between AHR and obesity or BMI [28, 30–36]. However, Chapman et al. found that after adjusting for the degree of airway closure, obesity did not appear to promote, but instead protect against the severity of AHR [37]. In a case-control study of 61 men who developed AHR during a 4-year follow-up compared to 244 control subjects, Litonjua et al. [38], observed that both low and high BMI at baseline were risk factors for the development of AHR. In a study of 300 adults, BMI was associated with the severity of AHR in allergic rhinitis and allergic asthma even whether these patients had a lower BMI than healthy controls [39]. Furthermore, not only is there no universal association between BMI and AHR, but also the degree of AHR does not seem related to the degree of obesity [30–32, 40–42].

The reasons for these different findings are uncertain, but it is possible that discrepancies between studies on the relationship between BMI and AHR are related to different subject characteristics such as age, gender, environmental exposures, diet, comorbidities, degree of obesity, or a combination of these characteristics. These findings may also vary according to the type of trigger, or etiologic factors; for example, compared with lean individuals, obese subjects have an increased response to stimuli such as ozone, with greater increases in airway responsiveness and greater decrements in lung function [43, 44].

How can obesity contribute to asthma?

Although asthma may promote weight gain through an increased sedentary life style and/or systemic corticosteroids usage, it does not explain the reported association of asthma and obesity. In the vast majority of subjects, obesity precedes asthma. Various mechanisms have been proposed to explain how obesity could promote the development of asthma [8, 45–47]. We will summarize these possible etiologic factors (Table 1).

Table 1. Mechanisms by which obesity can possibly influence the development of asthma

Influence on lung mechanics/function
Reduced FRC and tidal volume
Breathing at lower lung volumes
Reduced changes in airway calibre during efforts
Increased small airway closure
Loss of bronchoprotective effect of deep inspiration
Influence of obesity-associated systemic inflammation
Increased production of:
Pro-inflammatory cytokines (e.g. TNF α , IL6)
Chemokines (e.g. eotaxin)
Acute phase reactants
Increased oxidative stress
Increased leptin & reduced adiponectin levels
Increased prevalence of asthma-related comorbid conditions
Gastro-oesophageal reflux
Obstructive sleep apnoea/sleep disordered breathing
Diabetes, dyslipidaemia, hypertension
Depression
Common aetiological factors
Common genetic/ <i>in utero</i> -developmental influences
Dietary factors
Environmental influences/lifestyle/habits

FRC, functional residual capacity; TNF, tumour necrosis factor; IL, interleukin.

Developmental/genetic influences

An overlap in candidate genes and/chromosomal regions for obesity and asthma has been shown and it is possible that genetic characteristics influence obesity and asthma and/or mechanisms influencing the two conditions [46, 48–51]. Data obtained from 1001 monozygotic and 383 dizygotic same-sex twin pairs on self-reported physician diagnosis of asthma in obese subjects showed a strong association between their asthma and BMI with a significant heritability for asthma (53%) and obesity (77%), suggesting additive genetic influences on each disorder [50]. In another study of 29 183 Danish twins, genetic determinants of obesity and asthma were significantly correlated although only in women [52]. Further research is needed on the role of genetics in the relationship between asthma and obesity.

Mechanical changes

Obesity induces numerous changes in lung mechanics and function [53] (Fig. 1). The most obvious change is a reduction of the expiratory reserve volume (ERV), with an associated reduction in functional residual capacity (FRC), from changes in elastic properties of the chest wall as obese subjects breathe at lower lung volumes. Tantisira et al. found an inverse association between BMI and FEV₁/FVC ratio, but obesity is not considered to induce any significant airway obstruction [41, 53, 54]. However, when breathing at low FRC, airway calibre is reduced and

airway resistance can increase [54–57]. Breathing at low lung volumes may unload airway smooth muscle (ASM) and reduced breathing-related airway distension in the obese can theoretically increase airway responsiveness [41, 58–61]. This is supported by our previous observation that obese non-asthmatic subjects have lost the protective effect of a deep inspiration, observed in non-obese non-asthmatic subjects [62]. However, other mechanisms related to small airway closure may prevail to explain altered airway functions [59, 63]. Although these changes may favour the development of AHR, and increases in the prevalence of AHR in the obese have not been universally reported [33, 42, 64, 65]. Furthermore, bronchoconstriction increases lung hyperinflation in the obese compared with non-obese individuals [65], these effects being possibly due to increased expiratory flow limitation [66, 67] and increased airway closure [37].

Severe obesity may be associated to a reduced total lung capacity (TLC), with a restrictive pattern, but the residual volume (RV) usually remains unchanged [47, 68, 69]. Finally, obese subjects show an altered pattern of breathing, with higher breathing frequencies and reduced tidal volumes, even when exercising [53]. Obesity is associated with a reduction in respiratory system compliance, increased work of breathing and increased exercise-induced dyspnoea [53, 69].

Systemic/airway inflammation. Adipocytes may store and release a variety of inflammatory agents and obesity is generally considered as a low-grade systemic inflammatory condition [70, 71]. Increased levels of various inflammatory cytokines and mediators such as tumour necrosis factor- α (TNF- α), interleukin-6 (IL-6), eotaxin, vascular endothelial growth factor (VEGF), monocyte chemotactic protein (MCP) or markers of systemic inflammation such as C-reactive protein and serum fibrinogen have been observed in obese subjects [72]. Furthermore, levels of markers of oxidative stress such as

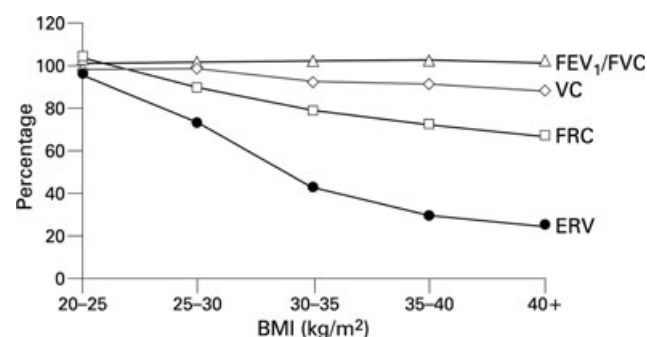


Fig. 1. Influence of obesity on lung volumes. Reproduced with permission from Sin and Sutherland [6]. FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; FRC, functional residual capacity; ERV, expiratory reserve volume.

8-isoprostane are increased in the blood and the lungs of obese compared to non-obese subjects [73].

Another characteristic of obese subjects is the presence of an increased number of leucocytes, particularly cytotoxic T cells and macrophages in the adipose tissue, possibly under the influence of hypoxia, chemoattractants or excess in lipid substrates [74–78]. Adipose tissue resident macrophages can produce a large variety of inflammatory molecules, which are increased in the presence of obesity [77].

A possible role of energy-regulating hormones has been suggested to explain the influence of obesity on asthma. In this regard, plasma levels of leptin, an IL-6 like adipokine secreted from adipocytes, are increased in obese subjects [79]. Leptin has multiple pro-inflammatory effects, and acts on the innate immune system [80–85], promoting chemotaxis and cytokine and surface markers of activation production [86–93]. Leptin can also increase alveolar macrophage activation [94, 95]. A link has been observed between leptin and asthma, particularly in children [96]. However, although leptin is closely related to obesity, its role in the development of asthma is unclear [97, 98].

Otherwise, the anti-inflammatory hormone adiponectin levels are lower than in non-obese subjects [96, 99]. Its levels increase with weight loss [100, 101]. Adiponectin, an insulin-sensitizing hormone, inhibits the production of pro-inflammatory cytokines by macrophages and monocytes and increases IL-10 and IL-1 receptor antagonist expression [102, 103].

Serum leptin and adiponectin concentrations have been independently associated with asthma in asthmatic subgroups [101–106], but the influence of obesity on asthma does not seem to be mainly mediated through the influence of these adipokines [99, 100]. A study looking at methacholine response in children showed no significant association between serum leptin or adiponectin and asthma [107]. The link between adipokines and asthma seems to be influenced by age and gender and associations are found in prepubescent boys, prepubescent girls, and premenopausal women for leptin and prepubescent girls and premenopausal women for adiponectin [108–111]. Furthermore, Engbers et al. found no correlation between plasma leptin concentration and airway inflammation, measured after an Adenosine Monophosphate (AMP) challenge [112]. In a Scandinavian prospective cohort study of children and adults, incident asthma was associated with obesity and prior weight gain, but there was no association between leptin, adiponectin, C-reactive protein, or insulin with asthma in a multivariate analysis [113]. Finally, Sutherland et al. showed that in obese and normal weight women with and without asthma, obesity was associated with increased interleukin (IL)-4 and IL-6, C-reactive protein, and leptin, and asthma was associated with C-reactive protein and Th₂-type

cytokines, but there were no obesity-by-asthma interactions [114]. Therefore, there are uncertainties on the link between obesity-related adipokines and airway inflammation or asthma [115].

In regard to airway inflammation, De Winter et al. showed that a higher BMI is associated with a higher eNO in healthy patients while Kazaks found no significant relationship between exhaled NO and BMI in adult asthma although there was no correction for use of corticosteroids [116, 117]. In another study, BMI and the ratio of leptin to adiponectin were, respectively, associated with reduced levels of exhaled NO [73].

We (L. P. Boulet, H. Turcotte, unpublished data) and Todd et al. found no significant difference in induced sputum cell differential in obese non-asthmatic compared to non-obese subjects globally [118] although we and Van Veen et al. found an inverse relationship between BMI and sputum eosinophils [30, 40]. Similarly, Barros et al. observed a negative association between BMI and Fractional exhaled Nitric Oxide (FeNO) in overweight or obese patients with asthma [119]. A recent report from Scott et al. suggested that there is an increase in neutrophilic airway inflammation in obese asthmatic female patients [120]. Furthermore, in cluster analyses, asthma in the obese patient was associated with a non-eosinophilic inflammatory phenotype [121].

The possible contribution of an increased oxidative stress in obese subjects on airways has also been studied. BMI is associated with increased levels of exhaled 8-isoprostanes [73] although systemic oxidant stress is not independently associated with asthma, suggesting that it does not explain the obesity-asthma association [122].

Finally, there are few studies on airway structure in obese patients with asthma. However, airway remodeling features, including smooth muscle mass area, sub-epithelial fibrosis and epithelium integrity seem to be similar between obese and non-obese asthmatic patients [123]. The existence of fat loculation on bronchial biopsies of morbidly obese subjects was suggestive of airway fat infiltration [63, 123]. The possibility that local fat can be a trigger for a local inflammatory process has, however, to be studied.

Can the increased prevalence of asthma in the obese be explained by atopy? Atopy is a major risk factor of asthma and previous studies have suggested that obesity could be a predisposition for the development of atopy [34, 35, 124, 125]. However, atopy does not seem to play a significant role in explaining the links between obesity and asthma. In fact, the opposite has been found, obesity being more often associated with non-allergic rather than allergic asthma in adults [102, 103, 105, 108–110, 126].

Diet. There has been an increasing interest about the effects of dieting on asthma, particularly among obese

patients. Fat and deficiencies in minerals (zinc, magnesium) or anti-oxidants have been associated with asthma and AHR [111, 115]. A high-fat, high-carbohydrate meal increases markers of oxidative stress in mononuclear cells isolated from peripheral blood, a feature that is enhanced in the obese [127]. Scott et al. had also shown that sputum % neutrophils was associated with total plasma saturated fatty acids and negatively with mono-unsaturated fatty acids in men [128]. Furthermore, glucose loading increased blood leucocytes and reactive oxygen species in circulating monocytes and neutrophils [129]. Caloric restriction promotes a reduction in weight and reactive oxidant species in subjects with asthma, in association with an improvement in expiratory flows and decreasing asthma symptoms, although which one between the two is responsible for this effect is uncertain [130].

Role of comorbidities. Comorbid conditions such as gastro-oesophageal reflux, OSA, diabetes, dyslipidaemia, and cardio-vascular diseases are more prevalent in the obese and may possibly influence the clinical expression of asthma, although a possible role in the development of the disease is not as obvious [28, 46]. In a study by Dixon et al. on 402 subjects (51% obese), those with a higher BMI reported a higher prevalence of reflux symptoms, but the prevalence of pH probe acid reflux was similar in all groups [131]. Reflux was not associated with measures of asthma control in obese patients. Furthermore, symptoms and self-report of OSA were more common with increasing BMI and associated with worse asthma control. So, Gastroesophageal Reflux Disorder (GERD) probably has little influence on asthma control in obese patients while OSA could, although in some studies, adjustment for these two conditions did not change the relationship between asthma and obesity [132, 133].

A possible role of the metabolic syndrome, characterized by the association of type 2 diabetes, systemic hypertension, dyslipidaemia, and central obesity has been suggested to explain the link between asthma and obesity. Leone et al. [134] found an independent relationship between reduced lung function and metabolic syndrome, mainly due to abdominal obesity and Lee et al. found that the metabolic syndrome was associated with asthma symptoms [135]. Furthermore, insulin resistance, often found in the obese, has been linked to allergen sensitization and asthma symptoms [136, 137].

Patients with morbid obesity (BMI > 40 kg/m²) have an increased prevalence of comorbid conditions such as hypertension, diabetes, congestive heart failure, asthma, poor functional status, sleep apnoea, pulmonary hypertension, venous thromboembolism, or venous oedema compared to leaner patients [138]. However, how comorbid conditions contribute to the development or

changes in the clinical expression of asthma in the obese subject remain to be explored.

What about the role of sedentary lifestyle?

We may think that the de-conditioning from lack of exercise could play a role in the relationship between obesity and the clinical expression of asthma. However, it was found that inactivity more than obesity was associated with higher asthma-related healthcare utilization [139]. Otherwise, low leisure time physical activity did not seem to explain the greater risk of asthma among obese men and women [125]. Finally, in another study, obesity was related to asthma independently of physical activity [140].

Pattern of obesity and asthma

In regard to the influence of the pattern of distribution of fat on airway function, the mechanical effect of obesity on lung function was found to be more strongly associated with central body fat distribution [141]. A more central-type of adiposity is particularly associated with obstructive lung function and functional impairment in men as compared to women [140, 142]. In regard to children, Garcia-Marcos et al. found that BMI, percentage body fat and skin fold thickness provided similar relationships with asthma in children aged 6–8 years [143]. However, in another paediatric study, waist circumference, waist/height ratio, and conicity as measures of central obesity were more strongly associated with asthma prevalence and severity than BMI [144]. Additional studies are needed on this subject.

Animal models. Studies on animal models show an influence of obesity on asthma and airway function. As reviewed by Shore, obese mice exhibit innate AHR, whatever the bronchoconstricting agent used, although it requires a significant increase in BMI to observe a heightened responsiveness [46]. Sensitized obese mice have a greater increase in airway responsiveness following allergen exposure compared to sensitized lean mice [44, 145]. Obese mice also exhibit greater ozone-induced increases in pulmonary resistance, airway responsiveness, and airway inflammation [146–149]. In animal models, administration of leptin increased allergen-induced AHR, but did not affect eosinophil influx [70]. Calixto et al. [150] also found in a murine model of asthma that diet-induced obesity enhanced eosinophil trafficking from bone marrow to the airway. Shore et al. also showed in lean wild-type and leptin receptor-deficient, diabetic, obese mice, that the administration of metformin did not affect ozone-induced airway inflammation [151]. However, whether these observations in animals can translate to humans is uncertain.

In conclusion, in animal models, adipokines derived from fat tissue seem to play a role in the relationship between obesity and asthma, although data are not as convincing in humans.

Can obesity influence the perception of respiratory symptoms?

Obesity is associated with increased respiratory symptoms and can potentially influence the assessment of asthma control [28, 152, 153]. In the case of obesity, weight gain can by itself be involved in generating respiratory symptoms or possibly enhancing asthma symptoms or their perception. Salome et al. showed no significant differences in the sensitivity or maximal response to methacholine between obese and non-obese subjects, but the intensity of dyspnoea was greater in obese subjects, associated with greater apparent stiffness of the respiratory system [65]. Engbers et al. also reported that the baseline perception of dyspnoea was higher in overweight patients, but during methacholine challenge, the perception of dyspnoea was lower in the overweight group, suggesting that bronchoconstriction was not as well perceived by overweight patients [112].

Perception of dyspnoea is mediated by several mechanisms including hyperinflation and increase in the work of breathing. In this regard, Sutherland et al. reported that after adjusting for baseline lung function, increases in FRC and decreases in inspiratory capacity (IC), suggestive of increased air trapping, were significantly greater in obese asthmatic women than normal weight asthmatic women during methacholine bronchoprovocation [31].

Dynamic lung hyperinflation, with increased end-expiratory lung volume (EELV) or reduced IC, correlates with dyspnoea scores in asthma [154]. Deesomchok et al. found that although baseline EELV was lower and IC was higher in obese compared to normal weight individuals with asthma, dyspnoea ratings were not different for a given FEV₁ or IC across groups [155]. In another study, perception of methacholine-induced bronchoconstriction and lung hyperinflation were also reported to be similar in obese and normal weight individuals with asthma [31]. However, individuals with a high BMI report exercise as an asthma trigger more often than those with a lower BMI [156].

Therefore, obese subjects seem to report more respiratory symptoms, but this does not seem to be due to their increased perception for a given change in lung function.

Asthma severity, control and response to therapy

Obese asthmatic compared to non-obese subjects report more frequent daytime and night-time symptoms and

limitation of social activities or exercise tolerance due to asthma [30, 156]. It has been suggested that obesity increases asthma severity [157–159] although its influence seems mainly to make asthma more difficult to control [30, 156, 160–162]. This may be due to a different asthma phenotype, to the added effects of obesity on respiratory symptoms or related to comorbid conditions (Table 2). Sastre et al. 2010 found a weak correlation between BMI and asthma control questionnaire (ACQ)-FEV1 although no correlation was found with ACQ without lung function or asthma control test (ACT) [163]. Surprisingly, a study found that obesity was associated with poor asthma control in mild-moderate, but not in severe asthma [164]. Furthermore, Taylor et al. showed that obese individuals with asthma had more severe symptoms and increased medication use [165].

Vortmann and Eisner also found that obese subjects with asthma who were recruited following hospital discharge in Northern California had increased symptoms and decreased asthma-specific quality of life when controlling for age, gender, race, income, and educational status, but did not find increased emergency health care utilization [166]. Mosen et al. and co-workers showed that obesity significantly affects symptoms, medication use, and quality of life, but that, in addition, obese individuals with asthma have a 4.6-fold increased risk of hospitalization for asthma compared with non-obese individuals with asthma in a multivariate analysis [157].

Poorer asthma control may be related to comorbid conditions, or to an altered response to treatment [162, 167]. We and others have shown that obesity is associated with a reduced response to asthma medications such as inhaled corticosteroids (ICS) as well as, particularly in presence of morbid obesity, to the association of an ICS and a long-acting bronchodilator [162]. The mechanisms underlying this reduced response are uncertain, but they may involve a different type of inflammation – asthma seems less eosinophilic with

Table 2. Potential factors involved in poorer control of asthma in the obese

Changes in lung mechanical properties
Increased work of breathing
Increased lung hyperinflation
Decreased thoracic compliance
Resistance to controller therapy
Less eosinophilic airway inflammation
Reduced glucocorticoid receptor response
Psychological factors
Anxiety/depression
Contribution of increased comorbidities
De-conditioning/sedentary lifestyle

increasing BMI – a reduced response of the glucocorticosteroid receptor, or other mechanisms [30, 168]. In another study, no relationship between BMI and either severity of asthma or healthcare use in children and adults was established, except in the latter where a higher BMI was associated with a significant reduction in quality of life (QOL) [169].

Finally, a sedentary lifestyle and de-conditioning may play key roles in the development of respiratory symptoms in obese asthmatic subjects. An improvement in asthma control in obese subjects was observed following a structured exercise programme, but it would be of interest to determine how asthma control changes after an exercise programme when no significant weight loss is achieved [170, 171].

Treatment of asthma in the obese

Obese asthmatic patients have altered responses to asthma medications. Peters-Golden et al. reported that obese asthmatics had an attenuated response to ICS, while obese and non-obese patients had a similar response to leukotriene antagonists [172]. In a study by Sutherland et al., fluticasone was statistically superior to montelukast for all BMI categories of normal, overweight, and obese subjects for FEV₁, morning peak flow, albuterol use, and symptom scores [173]. Fluticasone produced a significantly greater clinical response for normal, overweight, and obese subjects compared with montelukast.

A reduced beneficial response to ICS or to the association of ICS/long-acting bronchodilator combination medications was found in obese asthmatic subjects, but it was mostly prevalent among morbid obese subjects [162, 172] (Fig. 2). However, the beneficial effect was better with the combined therapy than montelukast alone [174]. Otherwise, Farah et al. reported that after 3 months of increased dosage ICS treatment, asthma con-

trol, spirometry airway inflammation, and AHR improved similarly across all BMI groups [175]. In regard to the reduced effect of corticosteroids, Sutherland et al. reported a reduced *in vitro* response to such agents in adults with moderate to severe asthma [168].

There is a possibility that inhaled medication does not reach the small airways in the obese, because of the altered lung function, although to our knowledge, there are no deposition studies on this. Furthermore, most inhaled medications are considered to work mainly in large to medium size airways. Moreover, compared to non-obese asthmatic controls, obese subjects have a worse asthma control with medications such as theophylline, an oral preparation [167].

Therefore, the optimal pharmacological treatment strategy for obese patients remains to be determined.

Obesity and asthma: a specific phenotype

Phenotyping asthma is considered to help understand better the various forms of asthma and adjust the treatment accordingly [176, 177]. We and others have suggested that “obesity-associated asthma” is different from asthma found in non-obese patients (Table 3) [30, 112, 178]. More recently, Engbers et al. suggested a new phenotype of mild controlled asthma in overweight women, showing a more marked systemic inflammation, while being less responsive to methacholine, but similarly responsive to AMP [112]. Cluster analyses of cohorts of asthma patients have also identified various sub-groups or phenotypes of asthma. In a US cohort of severe asthma patients, a unique group of mostly older obese women with late-onset non-atopic asthma, moderate reductions in FEV₁ and frequent oral corticosteroid use to manage exacerbations was identified [179]. Haldar et al. also reported that obesity and non-eosinophilic asthma is common across the spectrum of asthma severity [121].

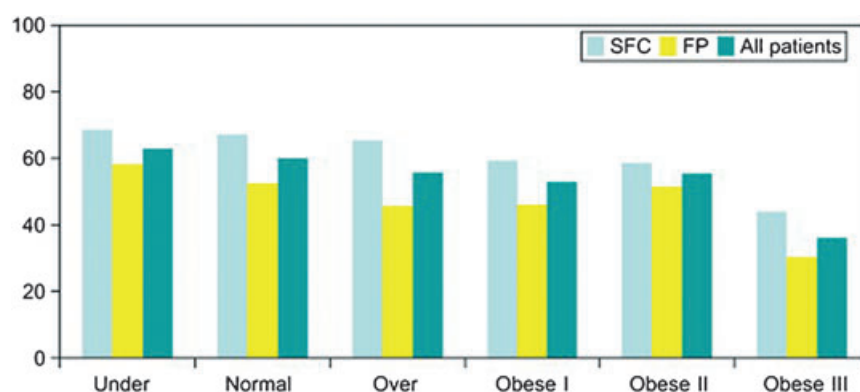


Fig. 2. Percentage of patients achieving good asthma control by fluticasone or fluticasone combined to salmeterol according to body mass index (BMI). Reproduced with permission from Varraso [158]. SFP, Salmeterol fluticasone propionate; FP, Fluticasone propionate.

Table 3. The "obesity-associated asthma" phenotype

- 1) Altered lung volumes (reduced ERV & FRC) and possible reduction in TLC in severe obesity)
- 2) Increased work of breathing and no increase in tidal volume on exercise
- 3) Weaker association between asthma clinical expression and AHR measurements
- 4) Weaker/no association with atopic status
- 5) Increased systemic inflammation and less eosinophil airway inflammation
- 6) More difficult-to-control asthma
- 7) Reduced response to asthma medications, particularly inhaled corticosteroids
- 8) Improvement of asthma after weight loss but despite no/small improvements in AHR or airway inflammation

FRC, functional residual capacity; ERV, expiratory reserve volume; TLC, total lung capacity; AHR, airway hyperresponsiveness.

Effects of weight loss on asthma

In the obese subject, even a modest weight loss is associated with a significant improvement of asthma and a reduced need for medication [180, 181]. Weight reduction from dieting and exercise can improve asthma symptoms, reduce peak expiratory flow variation, and improve spirometric values while bariatric surgery, for the most severe forms of obesity, yields the most remarkable results. In a meta-analysis of studies on weight loss and asthma in obese patients, Eneli found a universal improvement in asthma although what improved varied from one study and another [182]. In a study by Aaron et al. [183], for every relative weight loss of 10%, the FVC improved by 92 mL while the FEV1 improved by 73 mL although airway responsiveness did not significantly change with weight loss, suggesting that this latter change can improve lung function in obese women independently of changes in airway responsiveness. In patients with "refractory asthma", Bafadhel et al. reported that a 23% weight loss over a 1-year period improved lung function, but did not change asthma control or exacerbations [184].

Weight loss from a calorie-reduced diet has been associated with a reduction in markers of systemic inflammation [185, 186]. However, improvements in asthma control and expiratory flows do not seem to correlate with changes in either airway eosinophilic or neutrophilic inflammation [187].

In regard to bariatric surgery for asthma patients, an important weight loss has been associated with a significant reduction in medication needs, reduced symptoms, and improved general outcomes although in some of these studies, asthma was not objectively diagnosed [30, 188–191].

In a recent study, Dixon et al. studied 23 asthmatic and 21 non-asthmatic patients undergoing bariatric

surgery. After surgery, asthmatic participants had significant improvements in asthma control and asthma quality of life. Airways responsiveness to methacholine improved and the proportion of lymphocytes in bronchoalveolar lavage fluid and the production of cytokines from activated peripheral blood CD4(+) T cells increased significantly [192]. We also recently observed [193], improvements in AHR following bariatric surgery. However, the effects of a marked weight loss require further documentation to determine why asthma control is improved following such interventions.

Do current guidelines apply for the treatment of asthma in the obese patient?

Current guidelines, such as the Global Initiative for asthma provide a useful framework for the optimal management of asthma [193–195], but until recently, these guidelines had not yet specifically addressed how the recommendations may vary among the various asthma phenotypes. In regard to obese subjects, the current general guidelines are recommended, but we should be aware that obese subjects have a more difficult time controlling asthma and may not respond as well to current medications as other asthma subjects. Furthermore, asthma control criteria may not reflect the reality of obesity-related symptoms of asthma.

In obese asthmatic subjects, it seems reasonable to suggest that weight loss should be a priority as a therapeutic goal. In morbid obesity, bariatric surgery may be a valid option particularly as they usually have many other obesity-associated morbid conditions such as diabetes and are at risk of suffering from several other diseases. Furthermore, response to therapy should be closely monitored and treatment needs to be reassessed regularly. It would seem reasonable to suggest that obese patients should ideally be seen by a nutritionist, not only to help lose weight, but also to understand how to avoid diets high in glucose and fat and low in anti-oxidants, which may possibly have detrimental effects on the airways, although further evidence should be gathered to support these recommendations [196].

Conclusions – future research

Many questions remain in regard to the relationship between asthma and obesity; Table 4. It is now widely accepted that there is an increased prevalence and incidence of asthma in obese patients, but the question as to which of the various proposed mechanisms is key to explaining how obesity could influence the development of asthma needs to be examined. This effect is certainly multifactorial and may vary from one individual to another. There are also evidences that obesity complicates the control of asthma and that the beneficial

Table 4. Key-questions that remain to be answered on the relationship between asthma and obesity

- 1) What is the natural history of asthma in the obese?
- 2) What are the mechanisms and time-course of development of asthma in the obese?
- 3) Which are the genetic and epigenetic factors involved?
- 4) How do obesity-related mechanical changes influence the development and expression of asthma and is this influenced by the pattern of obesity?
- 5) What is the influence of the various patterns of distribution of body fat and of adipokines on asthma?
What is the role of comorbid conditions on this relationship?
- 6) What is the role of the diet on asthma in the obese?
- 7) What is the optimal management of asthma in the obese?
- 8) How should pharmacotherapy be used in these patients?
- 9) Should current asthma control criteria be modified in this population?
- 10) How can non-invasive measures of airway inflammation guide the treatment of asthma in these patients?

effects of asthma medication on obese asthmatic patients is reduced.

Obese asthmatic subjects may have a distinct phenotype of asthma, associated with a reduction in lung volumes, a less eosinophilic inflammation, altered response to asthma therapy, and poorer asthma control, while weight loss is associated with a universal improvement of asthma. The clinical implications of this change in phenotype on asthma management should be explored. Furthermore, the influence of the pattern of distribution of fat in the body on airway function and responsiveness should be examined. Asthma diagnosis and control require objective measures of airway function in the

obese particularly and the effects of therapy should be carefully examined. In these patients, weight loss should be a priority and the patients should be supported in their efforts to become closer to their ideal weight.

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