



The role of airway hyperresponsiveness measured by methacholine challenge test in defining asthma severity in asthma–obesity syndrome

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Purpose of review

Asthma is a complex disease defined by chronic inflammation of the airways. In research and clinical practice measures used for diagnosis, an assessment of control and severity of asthma are varied and there exists no gold standard. To date, several studies have explored the link between obesity and asthma although the exact mechanism is not yet fully understood. A study undertaken by our research group in 2015, on the effects of weight loss on asthma severity in obese asthmatics, demonstrated that an improvement in airway hyperresponsiveness could be achieved after significant weight reduction with a weight loss program. The objective of this article is to review the current literature for the primary and secondary outcomes studied to estimate the effects of weight loss on asthma severity in adults with obesity and asthma.

Recent findings

A review of the most recent research conducted since 2014 demonstrates that effects of weight loss on asthma severity in adults with obesity and asthma has not been the focus of majority of the studies. Apart from our study published in 2015, very few studies used airway hyperresponsiveness as the primary or secondary outcome measure. The literature reveals that significant weight loss does, however, lead to improvement in asthma severity and control in adults with obesity and asthma.

Summary

The current literature suggests that improvement in lung function requires moderate to significant (5–10%) weight loss in adults with obesity and asthma. However, with a few exceptions, the majority of these studies were small and used variable and questionable asthma severity outcome measures. There is an urgent need for standardization of diagnosis of asthma, study inclusion criteria, and outcome measures to assess asthma severity in research setting. Long-term effects of weight loss interventions on asthma severity and control, in adults with obesity and asthma, also remain unanswered.

Keywords

adherence, interaction, outcome, patient engagement, patient-oriented outcome

INTRODUCTION

Definition of asthma

According to the Global Initiative for Asthma (GINA) 2015 guidelines [1], ‘Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation.’

Diagnosis of asthma

The diagnosis of asthma relies on both presence of typical respiratory symptoms and quantifiable

reversible airflow obstruction or airway hyperresponsiveness (AHR). Following a medical history and physical examination suggestive of asthma, the current guidelines recommend using spirometry as a first step to confirm airflow obstruction and reversibility [1–3]. Obstruction is currently

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KEY POINTS

- Significant weight loss (5–10%) leads to improvement in asthma severity and control in adults with asthma–obesity syndrome.
- Outcome measures to estimate asthma severity in research are not standardized.
- Airway hyperresponsiveness measured by methacholine challenge test is the recommended outcome measure for asthma severity.

determined by forced expiratory ratio (FEV_1/FVC) of less than the lower limit of normal and reduced forced expiratory volume in 1 s (FEV_1), whereas, reversibility is defined by an improvement in FEV_1 of more than 12% and 200 ml either following β -agonist inhalation or after 4 weeks of anti-inflammatory treatment [1,4]. Alternatively, AHR can be evaluated by bronchial challenge test [3,4]. Other diagnostic investigations are also accepted such as variability in peak expiratory flow over 2 weeks, variability in FEV_1 between visits and positive exercise challenge test [1].

Novel investigations are suggested as alternative ways to achieve diagnosis of asthma. Oscillometry for instance, is a device that determines airway obstruction and resistance by emitting sound waves in the respiratory tract throughout the tidal respiratory cycle [5]. The main recognized advantage is that oscillometry is effort independent [6], however, it has not yet been recommended for the diagnosis, control or severity of asthma. Biomarkers such as fractional exhaled nitric oxide and sputum eosinophils are also gaining interest as diagnostic tools and control measures of airway inflammation, a key component of asthma [7,8]. However, both these biomarkers may have low sensitivity and specificity in diagnosis of asthma on their own [9].

Currently, there is no gold standard for the diagnosis of asthma. Furthermore, with the current guidelines and recommended diagnostic approach an extremely high rate of misdiagnosis exists [10,11] especially among obese individuals [12].

ASTHMA SEVERITY VS. ASTHMA CONTROL

Clinical studies and guidelines have used a range of outcome measures to assess asthma severity and control. There is no clear definition of asthma severity and often definitions of asthma severity are confounded with asthma control [3,13]. Effects

of weight loss on asthma severity and asthma control could be distinct in adults with obesity and asthma, thus there is an urgent need for clear definitions.

The terms asthma severity and control are used interchangeably [14] and measures used to define these terms have varied immensely. Multiple attempts have been made to differentiate severity and control of disease by, including both objective measures such as pulmonary function tests (PFT) and patient-reported outcomes. Asthma severity is defined as the difficulty to control the disease [4] or the intensity of the disease process [2]. The definition was conceptualized as a grading system to assist in asthma management and treatment. However, concerns were raised as classification of asthma severity did not take in consideration the fluctuating nature of the disease, access to treatment [14], treatment adherence, environmental exposures, or inhalation technique [15]. In an attempt to address these issues the WHO consultation workshop on severe asthma [14] clarified these definitions. Despite this effort, the definition and interpretation of asthma severity remain inconsistent.

Asthma control is more commonly used in the current guidelines [1,3]. It is defined as the improvement of the following with treatment: asthma symptoms, quality of life, and the risk of future adverse events [4]. The Canadian Thoracic Society includes the following: specific control criteria, day and nighttime symptoms, physical activity impairment, exacerbation, absence from work, need for rescue medication, FEV_1 or peak expiratory flow reduction [3].

Most asthma clinical studies use different outcome measures to define asthma severity or control making it difficult to compare and interpret clinical studies, because of inconsistencies in outcomes or inclusion criteria. Some asthma clinical studies have used AHR as a single outcome measure [16]. Bronchial challenge testing was first developed in the 1940s [17]. Since then, there have been numerous variations of the test before achieving standardized methods [18,19]. These standardized methods are highly sensitive but less specific for the diagnosis of asthma as AHR is not exclusive to asthma [9]. AHR is strongly associated with the clinical course of asthma [20] and can be used in both research and practice to determine if a patient with normal PFT has asthma [9]. However, despite its limitations, AHR, is one measure that correlates with asthma severity ([21,22] Cockcroft DW – personal communication).

PATIENT-REPORTED OUTCOME MEASURES

Outcome measures mainly focused on PFT were a norm [4]. However, with growing interest in integrating patient perspectives in research, there is a significant change of focus to incorporate patient-reported outcomes. In 2006, the Food and Drug Administration issued a document for guidance in development of patient-related outcome measures, to ensure higher quality tools for clinical studies [23]. Incorporating patient-related outcomes is also encouraged by the GINA guidelines [1].

OBESITY-ASSOCIATED ASTHMA

Asthma is a complex disease and numerous studies are shedding light on its different subtypes. Despite several studies [24,25] exploring the link between obesity and asthma, the pathophysiology is not fully understood. The proposed mechanisms include mechanical impairment from mass loading, chronic inflammatory state, comorbidities such as gastroesophageal reflux and obstructive sleep apnea (OSA) [1].

Obesity is defined as a BMI of over 30 kg/m². This excess in body mass in comparison to height contributes to a heavier chest wall and larger abdomen leading to increased inspiratory effort. Increased BMI can lead to decreased lung compliance [26] and decreased tidal volumes [27,28].

The systemic chronic inflammation in obesity may contribute to the asthma pathobiology. Specific proposed pathways include endocrine mediation through adipocytokines [29], increased oxidative stress [30], and alteration of eosinophil function [31].

ASTHMA–OBESITY INTERACTION

In 2010, our research group investigated the asthma–obesity interaction with the comparison of 242 obese to 254 normal weight adults with previously diagnosed asthma. Obese patients were more likely to be men, with more comorbidities and lower FEV₁ [32]. Subsequently, studies [33–35] have shown that asthma is harder to treat in patients with elevated BMI, demonstrated by poor responses to standard therapy and more frequent exacerbations. In a cross-sectional study assessing asthma control and comorbidities, Bruno *et al.* [25] divided 102 severe asthma patients in three groups according to BMI and confirmed that elevated BMI is associated with worst asthma control, type-2 diabetes, and OSA. Therefore, weight loss should improve asthma control. The 2014, GINA guidelines suggested

weight loss of 5–10% for asthma control among obese adults [1].

The objective of this article is to review the current literature for the primary and secondary outcomes studied to estimate the effects of weight loss on asthma severity among obese asthmatic adults.

RECENT FINDINGS

Outside the ‘healthy’ obese population, weight loss programs have been studied extensively [36]. The health benefits of weight loss among obese individuals are well recognized, although means to achieve weight loss goals and the optimization of weight-loss programs remain controversial and difficult to integrate in practice [36,37]. The main approaches to weight loss include surgical and nonsurgical options, such as diet, physical activity, behavioral, and medical therapies. Several studies focused on both surgical and nonsurgical weight loss programs for obese asthmatic adults.

A recent systematic review, including randomized control trials (until November 2014) concluded that weight loss would likely improve asthma outcomes although a threshold above 5–10% of weight loss was recommended [38]. These studies were mostly performed on small sample sizes and with short interventions; some used surgical and most nonsurgical interventions. Furthermore, asthma severity was not reported as an outcome in any study.

A prospective, controlled parallel-group study [39[¶]] performed by our research group enrolled 22 adults with obesity and asthma, 16 of which underwent an aggressive behavioral program, including caloric restriction. The other six served as controls. Asthma was objectively confirmed by the methacholine challenge test (MCT) to avoid misdiagnosis. An improvement in AHR was demonstrated and measured by provocative concentration of methacholine (PC₂₀) inducing 20% reduction in FEV₁ on MCT with a mean weight loss of 16.5 kg after 3 months. Thus, this study demonstrated that weight loss in adults with obesity and asthma can improve asthma severity measured by AHR (primary outcome), asthma control, lung function, and quality of life.

The Breathe Easier through Weight Loss Lifestyle study randomized 330 obese adults with uncontrolled asthma to usual care or a comprehensive 12-month weight loss intervention [40[¶]]. Recruitment was done through electronic health records where there was documented asthma-related healthcare usage suggestive of uncontrolled, persistent asthma. Diagnosis was further confirmed

by a physician, low asthma control test scores and confirmed reversibility of airway obstruction or evaluation of physicians' diagnosis through chart review. Usual care included a pedometer, scale and information about weight and asthma management. The treatment arm included an individualized, comprehensive lifestyle intervention with the target of moderate weight loss and increased physical activity level. The intervention group achieved a weight loss of 5 vs. 1% in the control group. There was no improvement in the primary outcome, asthma control questionnaire scores or secondary outcomes PFT and asthma exacerbations. The authors suggest that to improve asthma outcomes (mainly asthma control), a larger weight loss (>10%) may be required. Effect of weight loss on asthma severity was not estimated.

In a longitudinal study [41[■]], bariatric surgery led to significant weight loss in 39 obese asthmatics and 27 nonasthmatics in comparison with 12 obese asthmatic adults in the control group. However, they did not meet the primary outcome of improvement in FEV₁/FVC. Nonetheless, there was significant improvement in small airway function and asthma control. Importantly, this study measured and demonstrated significant reduction in bronchial inflammation, with the help of bronchial biopsies, performed at the baseline and at 12 months. Moreover, a small-subgroup of adults with obesity and asthma, with positive MCT at baseline demonstrated improvement in PC₂₀ (median 0.19–1.59 mg, $P=0.003$) in patients only with high IgE ('Th2-high', $n=12$), compared with those with low IgE ('Th2-low', IgE < 100, $n=6$) where there was no significant change in PC₂₀ (median 0.53–0.99 mg). Given this is a subgroup analysis of a small subset of the main study population, it is an interesting hypothesis generating idea. The absence of significant improvement in FEV₁/FVC is not surprising considering the lack of evidence for it as an asthma control or severity measure. Furthermore, it is not a recommended measure in the current guidelines [1,3].

Scott *et al.* [42[■]] followed 38 overweight or obese asthmatic adults and studied the effects of weight loss achieved by dietary restriction, exercise or combined dietary restriction and exercise. The primary outcome for this study was not clearly stated. However, it was demonstrated that the proportion of patients with AHR [measured as PD₁₅ (ml) (provocative dose) with bronchial provocation using 4.5% hypertonic saline nebulization with a standardized protocol] decreased significantly post-intervention in the combined group with dietary and exercise interventions (100 vs. 66.7% respectively, $P=0.027$). Interestingly, gynoid region adipose tissue (measured by dual-energy X-ray

absorptiometry) reduction was associated with reduced neutrophilic airway inflammation on sputum samples in women [b-coefficient (95% confidence interval); 1.75 (0.02, 3.48), $P=0.047$], whereas a reduction in dietary saturated fat was associated with reduced neutrophilic airway inflammation in men ($r=0.775$, $P=0.041$). The exercise intervention on the other hand demonstrated a significant reduction in sputum eosinophils [median (IQR); –1.3 (–2.0, –1.0)%, $P=0.028$]. This generates an interesting hypothesis that the obese-asthma phenotype may involve both innate and allergic inflammatory pathways.

In one non-English language study [43] asthma severity was measured with spirometry. This retrospective study focused on severity of acute asthma exacerbations rather than baseline asthma severity in obese compared with nonobese individuals demonstrating no difference. Another study [44], however, demonstrated that adults with asthma and obesity were at a higher risk of hospitalization because of acute asthma exacerbations compared with normal-weight adults with asthma.

DISCUSSION

The asthma–obesity syndrome is a growing concern. Although weight loss appears promising, it is complex to address. This problem of achieving and maintaining weight loss goes beyond physiology; it is multifaceted with political, structural, economic, environmental, and social aspects of obesity. (Fig. 1) Undoubtedly, it is important to tackle these issues as obesity is important in

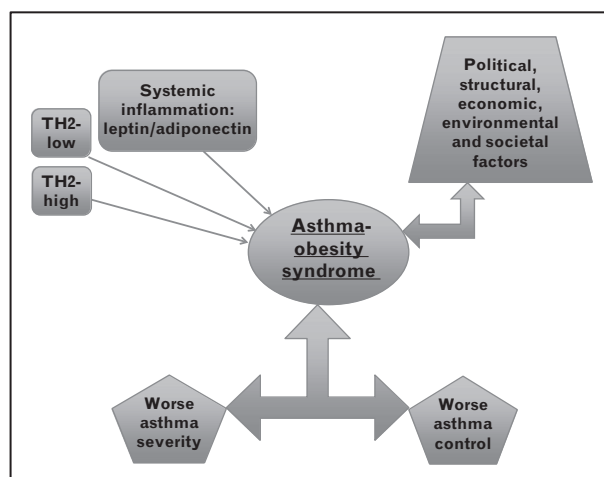


FIGURE 1. Asthma-obesity syndrome and its patho-physio-sociology. The not-yet-fully-understood complex relationship between asthma and obesity, thus, referred to as asthma-obesity syndrome, is described here with the available evidence.

management of not only asthma but multiple comorbidities such as diabetes, OSA and depression [45,46]. There are gaps in the current literature to elucidate the link between obesity and asthma and thus to optimize management.

First, asthma diagnosis, inclusion criteria and outcome measures in research studies require standardization. The use of more reliable measures in asthma would improve the quality of studies and allow more accurate comparison. The recent change of focus from objective outcome measures to patient-reported symptoms and quality of life encourages the use of patient-reported tools. Although multiple tools are currently available, it is suggested that further validation is still required [47].

AHR measured by MCT appears to be a promising asthma severity outcome measure as it is highly sensitive. However, the authors of a recent review [48] were unable to conclude that bronchial challenge testing was superior to the current outcome measures to determine asthma control. Nonetheless, these authors comment on its indispensable role in research such as assessing treatment efficacy.

Secondly, long-term outcomes of weight loss programs on asthma severity and control need further investigation. A significant number of weight loss interventions do not provide lasting effects [49]. With Heacock's suggestion that asthma control could be attained with diet independent of weight change [50], perhaps the long-term outcome would be positive without sustained weight loss. Furthermore, Scott *et al.*'s [42] findings showed that severe asthmatics are able to attain greater weight loss. This could suggest that the same population would also have more long-term success with weight management.

Finally, weight loss through surgical versus non-surgical methods should be examined separately and comparatively. It appears that both are successful in improving asthma severity and control as long as significant weight loss is attained. This suggests drastic, resource intensive, medically supervised weight loss programs are required. Other medical therapies also require further attention for obese asthmatic adults. Serafino-Agrusa *et al.* [31] reviewed the literature on medical therapies such as statins and bisphosphonates and concluded that diet and physical activity could achieve similar gains. Alternatively, pharmacotherapies could be selectively used in patients who are unwilling or unfit to undergo intensive weight loss programs or surgery.

CONCLUSION

Several researchers have investigated weight loss in adults with obesity and asthma as a treatment

strategy to improve asthma control. However, there are very limited studies exploring the effects of weight loss on asthma severity. The most recent studies support the findings from the previous ones, suggesting improvement in asthma severity and control requires moderate to significant weight loss in adults with obesity and asthma. However, asthma severity and control outcome measures remain unstandardized and a variety of outcomes measures are currently being used with minimal evidence of their ability to assess severity or control on their own. The need for a validated outcome measures to assess asthma severity and control thus remains. Despite its limitations, AHR is a recommended measure for asthma severity. In regards to the weight loss interventions in adults with asthma and obesity, many questions remain unanswered especially in the long-term setting.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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