Overweight is Associated with Airflow Obstruction and Poor Disease Control but Not with Exhaled Nitric Oxide Change in an Asthmatic Population

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Key Words
Overweight \cdot Airflow obstruction \cdot Disease control \cdot FeNO \cdot Asthma

Abstract
Background: The role of an elevated body mass index (BMI) in asthma remains controversial. Objectives: To investigate the relationship between overweight (BMI >25 and ≤30), lung function, disease control, and airway inflammation in an asthmatic population. Methods: We consecutively studied 348 patients (age 43 ± 16 years; 211 females). In all patients, BMI, spirometry, the Asthma Control Test (ACT), and fractional exhaled nitric oxide (FeNO; ppb) were measured. Results: One hundred forty-five patients were overweight and, as compared to those with normal BMI, had lower values of FVC, FEV\textsubscript{1}, and FEV\textsubscript{1}/FVC and of FEF\textsubscript{25–75} even when normalized for FVC (p < 0.05 for each comparison). The ratio between the number of patients with well-controlled asthma (ACT ≥20) and that of patients with poorly controlled asthma (ACT < 20) was significantly lower in overweight patients (1.07 vs. 1.84; χ\textsuperscript{2} = 6.030, p < 0.01). In overweight patients, the odds ratio of uncontrolled asthma expressed by logistic regression analysis was 1.632 (95% CI = 1.043–2.553), independently of gender, atopy, smoking habit, and inhaled steroid therapy. No difference was observed in FeNO values between overweight and normal weight patients (27.7 ± 2.3 vs. 27.9 ± 2.2 ppb). Conclusions: Our results show that, in an asthmatic population, overweight is associated with airflow obstruction and poor disease control but not with FeNO change. The findings of the present study support the view that other factors besides airway inflammation alone may explain the relationship between asthma and an elevated BMI.

Introduction

In Western countries, asthma and obesity are chronic and prevalent conditions [1]. Epidemiologic investigations have shown an association between obesity or an elevated body mass index (BMI) and prevalent and incident asthma [1]. However, the role of obesity in asthma control and severity remains unclear. As compared with normal weight patients, severe asthma was found to be more prevalent in obese patients [2], and obesity has been recognized as a risk factor for poor disease control [3].
the other hand, elevated BMI was associated with worse asthma control and quality of life but not with asthma severity [4]. Furthermore, among adults presenting to the emergency department with acute asthma, asthma exacerbations in obese and nonobese adults were similar [5]. Lastly, using four validated asthma control questionnaires, Clerisme-Beaty et al. [6] failed to find an association between obesity and asthma control in an urban population with asthma.

It is also worth noting that the value of airway inflammation in asthmatic patients with elevated BMI remains to be fully clarified [7]. Measurement of the fractional exhaled nitric oxide (FeNO), a reliable noninvasive marker of airway inflammation [8–11] which has become a clinical routine [12–14] in asthmatic patients, has provided conflicting results in patients with asthma when categorized by BMI. As compared with normal weight patients, obese asthmatic patients showed lower [15, 16] or similar [17, 18] FeNO values.

Discrepancies in reports on the asthma-obesity relationship may be partly due to the fact that obesity may be associated with lung volume changes and comorbidity, such as gastroesophageal reflux disease, which in obese patients may mimic asthma and may determine inaccuracy both in diagnosis and in severity grading of asthma. Notably, up to now, no study has been specifically addressed to investigate the relation between asthma and overweight, a condition in which the effects on lung mechanics as well as comorbidity are likely to be less remarkable than in morbidly obese patients.

The aim of the present study was to ascertain whether or not, in a large cohort of asthmatic patients recruited in an Italian tertiary care asthma clinic, overweight patients differ from normal weight patients both in terms of clinical and functional features and in terms of airway inflammation, assessed by FeNO measurement.

**Methods**

**Subjects**

Patients (14 years of age and older) with asthma diagnosis according to the international guidelines [19] were eligible to take part in the study and were prospectively recruited over an 18-month period, from April 2010 to September 2011, from our Asthma Outpatient Clinic. In each patient, BMI, duration of disease, smoking habit, and asthma therapy were recorded.

BMI was defined as the weight in kilograms divided by the square of the height in meters. In each subject it was calculated from patients’ self-reported height and weight. The international standard definition of obesity was used [20]. Patients were classified as underweight (BMI <18.5), normal (18.5 ≤ BMI ≤ 25), overweight (25 < BMI ≤ 30), or obese (BMI >30). The patients provided information on their duration of disease, smoking habit, and current medication use by completing a questionnaire.

Atopy was assessed by skin prick tests with a battery of 10 common inhalant allergens. All patients underwent FeNO measurement, completed the Asthma Control Test (ACT), and underwent spirometry as part of their visit.

The study was approved by the local ethics committee and all patients gave their informed consent.

**FeNO Measurement**

We ensured that the patients were not affected by any acute respiratory infection and had followed the pretest instructions, i.e. no nitrate-rich foods or beverages, including alcoholic ones, no tobacco smoking, and no exercise within 1 h preceding the test, as these factors can affect the test results. Moreover, all patients underwent FeNO measurement before the lung function test. Only patients able to perform at least two acceptable FeNO measurements were included in the analysis. FeNO was measured according to American Thoracic Society/European Respiration Society (ATS/ERS) guidelines [21] using an FeNO stationary chemiluminescence analyzer (NIOX; Aerocrine AB, Solna, Sweden).

All FeNO measurements were performed at the same time of day (±2 h) to allow a possible circadian rhythm effect. Patients were seated in the upright position without a nose clip and were asked to inhale nitric oxide-free air through a filter connected to the device deeply to total lung capacity and then to exhale for 10 s at a constant pressure guided by a visual cue to stabilize the flow rate. All tests were performed at an exhalation pressure of 10–20 cm H₂O to maintain a fixed flow rate of 50 ml/s. Measurements were repeated after a brief rest period until two acceptable values (±2.5 ppb for measurements <50 ppb and ±5% for measurements ≥50 ppb) were obtained (maximum six attempts). The mean of two adequate values for each subject was recorded for analysis. The system calibration was performed every 14 days.

**Asthma Control Assessment**

Asthma control was assessed using the Italian version of the ACT [22]. Patients subjectively evaluated the degree of impairment caused by their disease during the preceding 4 weeks by responding to five questions using a five-point scale. The ACT is reliable, valid, and responsive to changes in asthma control over time [22, 23]. The sum of the scores of the five questions gave the total ACT score (range 0–25). A cut-off score of 19 or less identifies patients with poorly controlled asthma.

**Lung Function Testing**

Lung function was measured by a flow-sensing spirometer connected to a computer for data analysis (CPFS/D Spirometer; MedGraphics, St. Paul, Minn., USA) which met the ATS standards. The forced vital capacity (FVC), forced expiratory volume in the first second (FEV₁), FEV₁/FVC ratio, and forced expiratory flow rate over the middle 50% of the FVC (FEF₂₅–₇₅) were recorded. FVC, FEV₁ and FEF₂₅–₇₅ are expressed as absolute values and as percents of predicted values [24], FEV₁/FVC is expressed as a percent.

**Statistical Analysis**

The distribution of variables was assessed by means of a Kolmogorov-Smirnov goodness-of-fit test. Variables are expressed as

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Means ± SD unless otherwise specified. Because of their non-Gaussian distribution, FeNO values were log-transformed before analysis and are expressed as geometric means with the corresponding standard error (SEGM). An unpaired t test, a Mann-Whitney test, Pearson’s χ² test, and ANOVA for repeated measures were used for comparisons when appropriate. To examine relationships between measures, Pearson’s correlation coefficient (r) and Spearman’s rank order correlation coefficient (rs) were used when appropriate. Logistic regression analysis was performed to test the association between the presence of overweight (dependent variable) and gender, smoking habit, atopy, poorly controlled asthma, and inhaled steroid treatment as independent variables. Odds ratios are presented with 95% confidence intervals. p ≤ 0.05 was considered statistically significant.

Results

Of the 422 patients who agreed to participate in the study, 14 had a BMI <18.5 (3.3%), 203 had a BMI ≥18.5 and ≤25 (44.6%), and 205 had a BMI >25 (48.6%). Of the 205 patients with elevated BMI, 145 were overweight (34.3%) and 60 were obese (14.2%). Underweight and obese patients were excluded from the study, leaving 348 patients suitable for the final analysis (table 1).

The overweight patients were significantly older than the patients with normal BMI (p < 0.001). The majority of patients were atopic (75%) with no difference between the two subgroups of patients (table 1). Patients with normal BMI did not differ from patients with increased BMI in terms of gender distribution, disease duration, and smoking habit (table 1). In the two subgroups of patients, the ratio between the number of patients treated with inhaled steroids and that of untreated patients tended to be significantly higher in overweight patients as compared to normal weight patients (104/41 vs. 130/73; χ² = 2.268, p = 0.082) (table 1). In all patients, spirometry ranged from a severe obstructive ventilatory defect to a normal value (FEV₁/FVC range: 45–98 % and FEV₁ range: 43–137%) (table 1).

The spirometry values were significantly lower in overweight patients as compared to the corresponding ones in normal weight patients (table 1). Notably, FEF₂₅₋₇₅ values, even when corrected for FVC, were significantly lower in overweight patients (table 1). Additionally, in all patients an inverse significant correlation was found between BMI and FEV₁ (r = −0.154; p = 0.004), FEV₁/FVC (r = −0.233; p < 0.001), and FEF₂₅₋₇₅ (r = −0.152; p < 0.005).

The ACT score was significantly different between overweight and normal weight patients (table 1). In the two subgroups of patients, the ratio between the number of patients with well-controlled asthma (ACT >20) and that of patients with poorly controlled asthma (ACT
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Discussion

The main finding of the present study is that overweight patients with asthma had worse spirometry and disease control as compared with normal weight patients, regardless of gender, smoking habit, and atopy. The percent of patients who were receiving inhaled steroids tended to be higher among overweight patients than normal weight patients. Importantly, no significant difference in airway inflammation, assessed by FeNO measurement, was found between the two groups of patients. Lastly, as has been reported in the Italian general population [25], we found that an increased BMI becomes more common with increasing age. Incidentally, our results indicate a high rate of obesity among adult asthmatics referred to an Italian tertiary care asthma clinic.

Physiologically, an elevated BMI may affect lung volumes, with no direct effect on airway caliber [26]. Spirometric variables, such as FVC and FEV1, tend to decrease with increasing BMI with no change or increase in FEV1/FVC [26]. Expiratory flows decrease with increasing weight in proportion to the lung volume, and in obese patients specific airway resistance, calculated by adjusting for the lung volume at which the measurement were made, is in the normal range [26]. Whether or not asthma and elevated BMI may interact on lung function has been little investigated so far. In a large group of subjects with normal values for airway function but a wide range of BMI, including subjects with a working diagnosis of asthma, Jones et al. [27] showed a significant linear relationship between BMI and lung volumes with no change in FEV1/FVC. The study did not provide any separate analysis for asthmatic and nonasthmatic subjects. In a large cohort of young adults aged 28–30 years, King et al. [28] found that after adjusting data for smoking and asthma, an elevated BMI was associated with reduced lung volume, which was in turn linked with airway narrowing as assessed by airway conductance. Interestingly, this study showed that the reduction in airway caliber was only partly related to the reduction in lung volume, suggesting other nonvolume-related mechanisms.

In this study, we found that flow-volume curve parameters, such as FVC, FEV1, and FEF25–75, were significantly lower in overweight asthmatic patients than in normal weight patients. Interestingly, when compared to normal weight patients, the reductions in FVC and in FEV1 were not affected to the same extent in overweight patients, since in these patients the FEV1/FVC ratio was significantly lower. In addition, even when corrected for FVC, the FEF25–75 values were significantly lower in overweight patients.

\[ \chi^2 = 6.030, p = 0.01 \] (fig. 1). In the whole study population, the ratio between the number of well-controlled and poorly controlled patients was 1.46. Moreover, in all patients ACT score values were inversely related to BMI values \((r = -0.170; p < 0.001)\). Logistic regression analysis showed that overweight was significantly associated with poorly controlled asthma, but not with gender, smoking habit, atopy, or inhaled steroids (table 2).

No difference was observed in FeNO values between overweight and normal weight patients (table 1), even when patients were further grouped according to BMI and inhaled steroid treatment. The geometric mean values (SEGM) of FeNO of overweight treated, overweight untreated, normal weight treated, and normal weight untreated patients were 27.4 (2.3) ppb, 28.5 (2.2) ppb, 27.6 (2.3) ppb, and 28.6 (2.2) ppb, respectively \((p = 0.783)\).

\(|\text{Table 2. Odds ratios (95% CI) by logistic regression analysis of female gender, smoking habit, atopy, inhaled steroid therapy, and poorly controlled disease for overweight patients with asthma}|\)

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>0.903 (0.577–1.412)</td>
<td>0.653</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>0.934 (0.508–1.718)</td>
<td>0.827</td>
</tr>
<tr>
<td>Atopy</td>
<td>0.735 (0.446–1.211)</td>
<td>0.227</td>
</tr>
<tr>
<td>Inhaled steroids</td>
<td>1.292 (0.803–2.081)</td>
<td>0.291</td>
</tr>
<tr>
<td>Poorly controlled asthma</td>
<td>1.632 (1.043–2.553)</td>
<td>0.032</td>
</tr>
</tbody>
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\(|\text{Fig. 1. Percent of asthmatic patients, categorized by BMI, with female gender, smoking habit, atopy, inhaled steroid therapy, and poorly controlled asthma. NW = Normal weight; OW = overweight. } \ast p = 0.012 \text{ by } \chi^2.\rangle|\)
patients. Taken together these findings indicate that overweight patients, as compared to normal weight patients, had a higher degree of both proximal and peripheral airflow obstruction, which was greater than expected on the basis of the reduction in lung volume.

The increased airflow obstruction, which we found in overweight patients, cannot refer to an increase in airway inflammation since FeNO values did not differ between the two groups of patients. Interestingly, asthmatic patients with elevated BMI as compared to normal weight patients do not appear to have increased airway cellular inflammation [29]. It also seems likely that the elevated BMI does not contribute to asthma through conventional Th type 2-mediated inflammatory pathways [29]. Dixon et al. [30] recently showed that, in obese patients with asthma, bariatric surgery does not reduce airway eosinophilia even though symptoms and airway hyperresponsiveness improve. In obese patients, it has been hypothesized that airway structures could be remodelled by exposure to pro-inflammatory adipokines or damaged by the continual opening and closing of small airways throughout the breathing cycle [29] and it cannot be excluded that even in overweight asthmatic patients these mechanisms may play a role.

Even when our patients were grouped considering both BMI and inhaled steroid treatment, we did not find any difference in FeNO values between overweight and normal weight patients. Previous studies on FeNO measurement in asthmatic patients categorized by BMI have provided conflicting results, with patients with increased BMI showing lower [15, 16] or similar [17, 18] values as compared to controls. It is also worth noting that in large samples of the general population neither weight [31] nor body fat [32] was significantly associated with FeNO values, whereas in smaller studies including obese patients with comorbidities [33, 34] an increase in FeNO values was associated with obesity. Discrepancies are likely to depend on the heterogeneity of the enrolled patients (e.g. severe obesity, a large range of BMI, comorbidities).

In the present study, overweight patients had worse disease control and tended to take more inhaled steroids as compared to normal weight patients. Patients with elevated BMI may experience wheezing and breathlessness due to their excess weight [35] and, consequently, may falsely attribute weight-related respiratory symptoms to asthma, causing increased medication use [36]. However, this explanation could be only partly taken into account for our results since overweight patients had a greater degree of airflow obstruction, to which the asthmatic symptoms could be attributed. In this context, it is conceivable that in overweight patients even increased inhaled steroid therapy, as compared to normal weight patients, was not enough to achieve disease control. It is important to note that an increase in BMI was associated with an increase in the delay/avoidance of health care [37]. In other words, in overweight patients behavioral factors could condition self-management both in terms of asthma control and in terms of diet and physical activity.

Previous studies provided discordant results on the relationship between asthma and elevated BMI, showing poor [3, 4] or similar [6] asthma control in obese patients in comparison to normal weight patients. Notably, studies showing poor control [3, 4] recruited patients in outpatient clinics, whereas the study showing no difference [6] recruited patients in community-based outpatient primary care practices. Moreover, there are some differences between these studies and ours. These studies [3, 4, 6] were mainly addressed to obese patients and did not provide any information on the airway inflammation of the patients. Notably, only in one study [4] were the patients assessed by spirometry, which showed a reduction of FVC values in obese patients when compared to normal weight patients.

As compared to the Italian general population [25], in our cohort of patients we found a higher rate of obese patients. Our data are consistent with the results of a previous Canadian report [4] and suggest that in industrialized countries obesity may be more common among adult tertiary care asthmatics than in the general population. This finding could be due to the fact that asthmatic patients followed at a tertiary care hospital may be more likely to have comorbidity than patients followed by primary care physicians.

We acknowledge that this study has some limitations. Firstly, we defined normal weight and overweight only in terms of BMI and we cannot exclude that other measures of excess body weight, such as the waist-hip ratio or waist circumference, might better clarify the impact of increasing body fat on asthma. However, which is the best risk factor among adiposity measures is still debatable [38]. Additionally, we calculated the BMI using self-reported height and weight. It has been reported that, despite the high correlation between measured and self-reported data, the prevalence of overweight calculated from measured values is higher than that calculated from self-reported values among older adults [39]. When calculated based on a self-reported height, the BMI was one unit lower than when calculated from a measured height for persons older than 70 years [39]. As most of our patients were young adults (median age 41 years, 30–54 years 25–
75% percentile), we are confident in our estimates of BMI. Finally, in this study we did not record the comorbidities of our patients, such as gastroesophageal reflux disease, which could be a confounding factor in asthmatic patients with elevated BMI. However, it is conceivable that overweight is a condition in which the comorbidities might play a less remarkable role than in morbidly obese patients.

In conclusion, although we cannot infer any cause-effect relationship between adiposity and clinical and functional features of asthma from our data, the present study shows that preobese asthmatic patients are at an increased risk of airflow obstruction and poor disease control. This study also supports the view that factors other than airway inflammation alone may explain the relationship between an elevated BMI and asthma and further underlines the relevance which behavioral factors may have in the management of asthma.

Financial Disclosure and Conflicts of Interest
The authors have no conflict of interest.


