Airway inflammation in obese and nonobese patients with difficult-to-treat asthma

**Background:** Asthma and obesity are associated disorders, but the contribution of obesity to difficult-to-treat asthma as well as the mechanisms responsible for this relationship is unclear. The aim of this study was to investigate the relationship between obesity (body mass index ≥ 30) and factors related with asthma severity in patients with difficult-to-treat asthma.

**Methods:** One hundred and thirty-six nonsmoking asthmatic adults with persistent symptoms despite high doses of inhaled or oral corticosteroids and long-acting bronchodilators were studied [70% female, median (range) age 44.6 (18–75) years, 32% on daily oral corticosteroids]. The association between obesity, lung function parameters [forced expiratory volume in 1 s (FEV₁)], functional residual capacity/total lung capacity (FRC/TLC)], inflammatory markers [blood eosinophils, sputum eosinophils and neutrophils, exhaled nitric oxide (FENO), airway hyperresponsiveness, C-reactive protein (CRP)] and aggravating co-morbid factors (severe chronic sinus disease, gastro-esophageal reflux, recurrent respiratory infections, psychopathology and obstructive sleep apnea) was investigated.

**Results:** Obese patients (n = 29) had a higher FEV₁%pred (P = 0.05) and a lower FRC/TLC%pred (P < 0.01) compared with nonobese patients (n = 107). Body mass index was inversely related with sputum eosinophils (r = −0.36, P < 0.01) and FENO (r = −0.30, P < 0.01). Obese patients had an increased risk for gastro-esophageal reflux (OR = 2.3) and sleep apnea (OR = 3.1).

**Conclusion:** Obesity in patients with difficult-to-treat asthma is inversely related with sputum eosinophils and FENO, and positively associated with the presence of co-morbid factors and reduced lung volumes. This suggests that other factors than airway inflammation alone explain the relationship between obesity and asthma severity.

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Methods

Subjects
One hundred and thirty-six patients, aged 18–75 years, with difficult-to-treat asthma according to the definition of the European Respiratory Society Task Force (9), were consecutively recruited from the outpatient pulmonary departments of 10 hospitals in the western region of the Netherlands. The participating patients had a history of episodic dyspnoea and wheezing, a documented (recently or in the past) reversibility in FEV₁ > 12%pred and/or hyperresponsiveness to inhaled histamine. Patients were all treated with ≥1600 μg/day beclomethasone or equivalent and long-acting bronchodilators for >1 year, and were all nonsmokers (smoking history ≤10 pack-years). They were all symptomatic and had experienced at least one severe exacerbation during the past year requiring a course of oral corticosteroids or were on maintenance therapy with oral prednisone. The study was approved by the Hospital Medical Ethics Committee, and all patients gave written informed consent. Previous investigations in this patient cohort have been published elsewhere (10–12).

Measurements

Lung function parameters. Forced expiratory volume in 1 s (FEV₁) was assessed before and 30 min after the inhaled administration of 400 μg salbutamol and 80 μg ipratropium bromide. Functional residual capacity (FRC) and total lung capacity (TLC) were measured by the multiple-breath helium equilibration method. All lung function parameters were expressed as percentage of predicted value (13).

Markers of systemic and airway inflammation. Eosinophils in blood were measured by standard automated cell counter. Sputum was induced and processed according to a validated protocol (14), using the ‘full sample’-method. Saline solutions were inhaled three times for 5 min with frequent monitoring of the FEV₁. Differential cell counts were performed on cytospins. Exhaled nitric oxide measurements were performed by standardized method (15), using a chemiluminescence analyzer (Sievers NOA 270B; Boulder, CO, USA). After inhaling ‘NO-free’ air (<2 ppb) from residual volume to TLC, subjects performed a slow expiratory vital capacity manoeuvre with a constant expiratory flow rate of 100 ml/s (standard at the time of study initiation). Plateau levels of FE(NO) against time were determined and expressed as parts per billion (ppb).

Airway responsiveness to histamine, expressed as provocative concentration to cause a 20% fall in FEV₁ (PC20 histamine) was measured using a tidal breathing standardized procedure (16). High sensitivity CRP (hs-CRP) in blood was measured by enzyme-linked immunosorbent assay, with a lower detection limit of 0.5 mg/l.

Aggravating co-morbid factors. Paranasal sinus disease was considered a potential aggravating factor, if there was an indication for functional endoscopic sinus surgery, as judged by an independent ENT specialist. For this purpose, nasal endoscopy and standardized CT-scanning was performed.

Gastro-esophageal reflux was demonstrated by a 24-h pH measurement of the oesophagus (17) or dependency on proton-pump inhibitors. Recurrent respiratory infections were defined as more than or equal to three episodes in the past 2 years of increased dyspnoea, cough and purulent sputum for which antibiotic courses were prescribed.

Psychological dysfunctioning was defined as a score ≥6 on the short General Health Questionnaire (GHQ-12) (18). Obstructive sleep apnea was assessed by polysomnography, or by heavy snoring and frequent apnea periods of >10 s (19) reported by the partner in combination with a history of daytime sleepiness.

Analysis

Blood eosinophils, sputum eosinophils and neutrophils, FE(NO) and PC20 histamine were log-transformed before analysis to achieve a normal distribution. Differences in obese (BMI ≥30) and nonobese (BMI < 30) patients were analysed using unpaired t-tests, chi-squared analyses and nonparametric tests, wherever appropriate. Uni- and multivariate regression analysis (with age, sex, atopy, FEV₁ and oral corticosteroid dose as independent factors) was used to assess associations between BMI and parameters of lung function (FEV₁, FRC/TLC) and airway inflammation (blood and sputum eosinophils and neutrophils, FE(NO), PC20 histamine and hs-CRP).

The regression line was described by the correlation coefficient (r) and the slope of the regression line (B). Logistic regression analysis was performed to determine whether there was an association between the presence of obesity (independent factor) and the presence of each of the five co-morbid factors (dependent factor). Odds ratios with 95% confidence intervals (CI) were obtained. All analyses were performed using the Statistical Package of the Social Sciences (spss version 12.0). The P-values < 0.05 were considered statistically significant.

Results

Comparison between obese and nonobese patients

Obese patients (BMI ≥30, n = 29) did not differ from those with BMI < 30 (n = 107) with respect to age, atopy, age of asthma onset and medication dose. There was a trend (P = 0.06) for a longer duration of asthma in the obese patients. Obese patients had a higher FEV₁%pred than nonobese patients and a lower FRC/TLC %pred (Table 1). Patients with a high BMI (≥30) had a lower percentage of sputum eosinophils and sputum neutrophils and lower FE(NO) values as compared with patients with BMI < 30. High sensitivity-CRP was higher in obese as compared with nonobese patients. There was no difference in blood eosinophils or airway responsiveness between the two groups (Table 2).

Table 1. Clinical and lung function characteristics in obese vs nonobese patients

| Age (years) | 44.8 (15.0) | 47.4 (11.4) | 0.39 |
|Sex (% female) | 68.2 | 75.9 | 0.43 |
|Age of asthma onset* (years) | 17.5 (0.5–68) | 8.0 (0.5–54) | 0.37 |
|Asthma duration* (years) | 17 (2–73) | 27 (6–57) | 0.06 |
|Ex-smoker (%) | 36.4 | 48.3 | 0.25 |
|Atopy (%) | 55.8 | 65.5 | 0.35 |
|Inhaled steroids (μg/day)* | 1600 (1600–6400) | 1600 (1600–4000) | 0.88 |
|Daily oral steroids (%) | 33 | 31 | 0.84 |
|FEV₁ %pred | 75.8 (24.3) | 85.9 (23.0) | 0.05 |
|FEV₁/VC %pred | 79.1 (20.0) | 84.9 (17.6) | 0.17 |
|FRC/TLC %pred | 117.7 (31.0) | 100.3 (25.6) | 0.009 |
|BMI* | 24.4 (17.5–29.9) | 32.7 (30.1–44.9) | <0.001 |

BMI, body mass index; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; FRC, functional residual capacity; TLC, total lung capacity.

Data in mean (SD) or *median (range) or percentage of patients having the factor. %pred denotes percentage of the predicted value.
Table 2. Inflammatory characteristics in obese vs nonobese patients

<table>
<thead>
<tr>
<th></th>
<th>BMI &lt; 30 (n = 107)</th>
<th>BMI ≥ 30 (n = 29)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood eosinophils (10⁹/l)</td>
<td>0.21 (0–1.35)</td>
<td>0.15 (0.01–0.83)</td>
<td>0.13</td>
</tr>
<tr>
<td>Sputum eosinophils (%)</td>
<td>2.8 (0–69.4)</td>
<td>0.5 (0–12.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Sputum neutrophils (%)</td>
<td>72.0 (11.6–97.4)</td>
<td>54.6 (33.5–94.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>FENO (ppb)</td>
<td>11.1 (2–202.3)</td>
<td>7.2 (2–35.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>PC20 histamine (mg/ml)</td>
<td>1.31 (0.02–6)</td>
<td>1.91 (0.02–8)</td>
<td>0.04</td>
</tr>
<tr>
<td>hs-CRP (mg/l)</td>
<td>2.5 (0.5–65.3)</td>
<td>8.1 (0.5–53.7)</td>
<td>0.003</td>
</tr>
</tbody>
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BMI, body mass index; FENO, exhaled nitric oxide; PC20, provocative concentration to cause a 20% fall in FEV1; hs-CRP, high sensitivity CRP. Data in median (range).

Table 3. Co-morbid factors in obese vs nonobese patients

<table>
<thead>
<tr>
<th></th>
<th>BMI &lt; 30 (n = 107)</th>
<th>BMI ≥ 30 (n = 29)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe chronic sinus disease (%)</td>
<td>37.5</td>
<td>36.8</td>
<td>0.96</td>
</tr>
<tr>
<td>Gastro-esophageal reflux (%)</td>
<td>44.9</td>
<td>65.5</td>
<td>0.05</td>
</tr>
<tr>
<td>Recurrent respiratory tract infections (%)</td>
<td>55.1</td>
<td>69.0</td>
<td>0.18</td>
</tr>
<tr>
<td>Psychopathology (%)</td>
<td>16.9</td>
<td>32.0</td>
<td>0.10</td>
</tr>
<tr>
<td>Obstructive sleep apnea (%)</td>
<td>9.3</td>
<td>24.1</td>
<td>0.05</td>
</tr>
</tbody>
</table>

BMI, body mass index. Data in percentage of patients having the factor.

Obese patients had a higher total number of co-morbid factors as compared with nonobese patients [median (range): 3 (1–4) vs 2 (0–4), P < 0.01]. Of the five investigated co-morbid factors, gastro-esophageal reflux and obstructive sleep apnea were more prevalent among the obese patients as compared with the nonobese patients (Table 3). Although the percentage of patients with psychopathology was not significantly different between both groups, obese patients had higher overall GHQ scores than nonobese patients [median (range): 3.0 (0–12) vs 1.0 (0–12), P = 0.03].

Association between obesity and parameters of asthma severity

Linear regression analysis showed a negative association between BMI and sputum eosinophils (r = –0.36, B = –0.03, P = 0.003) and BMI and FE NO (r = –0.30, B = –0.03, P = 0.005) (Fig. 1). These associations remained in the multivariate regression analysis after adjustment for age, sex, atopy, FEV1 and oral corticosteroid dose (r = –0.40, B = –0.03, P = 0.02 and r = –0.33, B = –0.03, P = 0.01 respectively). Multivariate regression analysis including the same co-variates showed a positive association between BMI and hs-CRP (r = 0.50, B = 0.42, P < 0.01) and a negative association between BMI and FRC/TLC (r = –0.84, B = –1.3, P < 0.01).

Logistic regression analysis showed that obese patients had a 2.3-fold (CI: 1.0–5.5) increased risk for gastro-esophageal reflux and a 3.1-fold (1.1–9.0) increased risk for sleep apnea (Fig. 2).

Discussion

In this study, obesity in patients with difficult-to-treat asthma was not associated with more severe airway inflammation or more airway obstruction, but was related to reduced lung volume and to the presence of aggravating co-morbid factors. Body mass index was negatively associated with sputum eosinophils and FE NO, and obese patients had an increased risk of gastro-esophageal reflux (2.3-fold) and obstructive sleep apnea (3.1-fold). These results suggest that obese patients with difficult-to-treat asthma represent a group of patients that may require a specific treatment approach.

The negative association between BMI and sputum eosinophils and FE NO is in contrast with previous findings in a population-based cohort where no relation was found between obesity and FE NO (20). Interestingly, a short communication describing a group of patients with mild asthma also showed a negative association between BMI and FE NO (21) which supports our findings in difficult-to-treat asthmatic patients.

Our study also shows that obese patients with difficult-to-treat asthma had more co-morbid factors than nonobese patients, in particular gastro-esophageal reflux and sleep apnea. Obesity has been related with a higher prevalence of several co-morbid factors in the general population. van Veen et al.
population (22-24) and the presence of co-morbid factors has been related with more severe asthma (12, 25, 26). This study extends these findings by linking obesity to co-morbid factors in patients with difficult-to-treat asthma.

In the present study, there was a trend for a longer asthma duration in the obese patients as compared with the nonobese. A previous study in persistent asthma did not find a difference in asthma duration between overweight patients and those with normal BMI (4). It might be possible that in our study group life-long asthma and prolonged use of corticosteroids have contributed to the development of obesity. Taken together, a low level of airway inflammation and the presence of aggravating co-morbid factors seem to characterize the obese patient with difficult-to-treat asthma.

We do not think that the results of our study are influenced by selection bias or inadequate methodology. All patients, obese as well as nonobese, fulfilled the same strict selection criteria for difficult-to-treat asthma (9). They had a firm diagnosis of asthma, based on a history of episodic dyspnoea and wheezing, hyperresponsiveness to inhaled histamine (PC20 < 8mg/ml), and or a documented bronchodilator reversibility in FEV1 > 12%pred. They were symptomatic despite the use of high doses of asthma medication, and had experienced a severe asthma exacerbation during the year before entering the study. Airway inflammation was measured by cell differential counts in induced sputum and the level of nitric oxide in exhaled air. These measurements are now widely accepted as reliable non-invasive tools to assess airway inflammation in asthma (27, 28). One could argue that adherence to oral corticosteroids might have influenced our results, as adherent patients are likely to have less airway inflammation and a higher BMI. However, we do not believe that this was an important confounding factor, because oral steroid dependent patients only represented one-third of the total group, and the association between obesity and airway inflammatory markers remained significant after adjustment for oral corticosteroid dose.

Our finding of less severe airway inflammation in obese patients with asthma may be unexpected. Several studies have demonstrated persistent low-grade systemic inflammation in obese individuals compared with lean subjects as indicated by higher circulating levels of amyloid A, fibrinogen, tumour necrosis factor alpha and CRP. Also in our study, CRP levels were increased in the obese patients. It has been suggested that high levels of pro-inflammatory molecules released from adipose tissue into the systemic circulation could contribute to airway inflammation, thereby increasing the prevalence and severity of asthma in the obese (29). Although cross-sectional and prospective cohort studies in humans have indeed demonstrated a modest overall increase in asthma prevalence and severity in the obese, our results do not support the hypothesis that this is caused by enhanced airway inflammation. Our study rather suggests that altered lung volumes and a higher prevalence of co-morbid factors are the mechanism whereby obesity contributes to increased asthma severity. A decrease in FRC as observed in the obese patients in our study not only causes shallow breathing and increased dyspnoea sensation, but might also enhance airway responsiveness by unloading of the airway smooth muscle. Furthermore, an increased prevalence of obesity related co-morbid factors, such as gastro-esophageal reflux and sleep apnea are also likely to contribute to more severe asthma symptoms.

Our study has pathophysiological and clinical implications. It shows that low-grade systemic inflammation as observed in obese patients is not necessarily associated with enhanced airway inflammation. The finding of less severe airway inflammation in the obese patients suggests that their underlying asthma may in fact be milder. This raises the hypothesis that the effects of the adipose tissue on lung function or the presence of co-morbid factors make them more symptomatic and difficult-to-treat. If so, weight reduction in obese patients might improve asthma control by reducing the impact of co-morbid factors and by attenuating the negative effects on lung volumes. Studies have indeed shown that weight reduction programmes reduce symptoms in patients with asthma (30).

In conclusion, our study has shed new light on the association between obesity and asthma severity. Obese patients with difficult-to-treat asthma do not have more airway inflammation as compared with nonobese patients. On the contrary, they have higher FEV1 and less airway inflammation. The results of our study fit in with the hypothesis that obese patients with asthma may exhibit more severe asthma symptoms or even become difficult-to-treat because of an unfavourable effect of overweight on lung function, or because of aggravating
co-morbid factors including gastro-esophageal reflux and obstructive sleep apnea. The therapeutic approach of obese patients with difficult-to-treat asthma should therefore not be primarily focused on intensifying anti-inflammatory treatment but rather on weight reduction and adequate control of co-morbid factors.

Acknowledgements

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References