

OBESITY

Obesity and Poor Asthma Control in Patients with Severe Asthma

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Background. Asthma is a public health problem as it leads to hospitalization and eventual death, particularly in its severe forms. Many studies have demonstrated an association between obesity and asthma. **Objective.** The aim of this study was to investigate the relationship between obesity and asthma control in a group of patients at a reference center for severe asthma in Brazil. **Methods.** This cross-sectional study was conducted in the outpatient central reference clinic of the Program for Control of Asthma in the State of Bahia. It included 508 subjects with severe asthma of both genders and above 18 years of age. All the participants answered a sociodemographic and a clinical questionnaire to collect information on their asthma and comorbidities, such as rhinitis and gastro-esophageal reflux disease (GERD). Participants also completed the Asthma Control Questionnaire, performed a spirometry test, and had their weight, height, and waist and hip circumferences registered. **Results.** Logistic regression analysis demonstrated a positive association between body mass index (BMI) and uncontrolled asthma [odds ratio (OR) 1.5; 95% confidence interval (CI) 1.02–2.20]. Symptoms of chronic rhinitis and GERD were also significantly associated with uncontrolled asthma (OR 3.68, 95% CI 1.50–9.01; and OR 2.78, 95% CI 1.91–4.03, respectively). There was no correlation between waist-to-hip ratios and asthma control. **Conclusion.** In our sample of patients with severe asthma, those who were obese were more likely to have uncontrolled asthma than patients with a normal BMI. Nevertheless, this is not conclusive evidence for a direct causal association between obesity and poor asthma control. Future studies are necessary to dissect the relationship between obesity and asthma outcomes.

Keywords asthma control, obesity, body mass index, gastro-esophageal reflux disease

INTRODUCTION

Asthma is a public health problem as it leads to hospitalization and eventual death. Despite sound advances in diagnosis and treatment, its prevalence has increased worldwide during the previous decades (1). In Brazil, recent estimates predict that more than 16 million people (2) have asthma, and among these, we estimate that 10% have the severe form of the disease. A national health database in Brazil has stated that asthma is one of the leading causes of hospitalizations in the country (2). Although in the minority, those with severe asthma demand the majority of the government's health service resources (3–5).

The main objective of asthma treatment is the control of symptoms, which reduces the risk of further morbidity and mortality. Optimal control is defined by the absence of exacerbations, no night awakening due to asthma, no limitations on physical activities, and normal pulmonary function (6). Optimal control can be achieved with proper treatment. Several factors may be related to poor asthma control, such as environmental factors, psycho-social and

genetic conditions, and comorbidities (7). There is some evidence that obese asthmatics are more likely to have uncontrolled asthma (8).

Obesity has also been associated with increased risk of asthma (9) and asthma severity (10). A longitudinal study reported improvement in lung function after weight loss for obese asthmatics (11). The presence of abdominal fat reduces the lung volume, changing the respiratory physiology. Adiposity also affects the performance of diaphragm, leaving it susceptible to fatigue during dynamic stress.

A causal relationship between obesity and asthma has not been established. The use of inhaled and oral corticosteroids in subjects with asthma may contribute to weight gain and obesity which can ultimately promote a functional deterioration of asthma (12, 13).

Although many studies have demonstrated the possible association between obesity and asthma, this discussion is still controversial and requires further evidence to be fully understood. The objective of this study was to investigate the association between obesity and poor control among subjects with severe asthma.

MATERIALS AND METHODS

The Program for Control of Asthma in Bahia—Prioritizing Severe Asthma

This study was conducted in the Central Reference Clinic of the Program for Control of Asthma in Bahia (ProAR),

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founded in 2002 through collaboration among the Federal University of Bahia, the Departments of Health of the City of Salvador and of the State of Bahia, and the Brazilian Ministry of Health. ProAR is composed of four reference centers for multidisciplinary care, pharmaceutical assistance, and patient education. The reference clinics are accessible to all individuals free of charge. Within ProAR, priority was given to the treatment of severe asthma, and patients were treated with regular use of combined inhaled corticosteroids (beclomethasone or budesonide) and a long-acting beta-2 agonist (formoterol), plus a short-acting inhaled beta-2 agonist (salbutamol or fenoterol), as needed, in accordance with current international guidelines (6).

Subjects with severe asthma who were admitted to ProAR were referred by general practitioners and hospitals, emergency room specialists, and ICU specialists. Additionally, a clinical screening, prior to admission, has been routinely performed to avoid misclassification and misdiagnosis of asthma. Patients with a history of smoking or former heavy smokers were not enrolled in the program in agreement with an act of the Ministry of Health of Brazil for pharmaceutical assistance in asthma.

Over 3000 asthmatics were admitted and regularly participated in this program. The program aims to prevent asthma exacerbation and reduce hospitalization and mortality and was targeted at severe asthma due to the lack of available resources to address issues at all levels of care. A rapid reduction in the utilization of health resources among subjects enrolled in the program and a 74% reduction in asthma-related hospitalizations within the public health system for the entire population of Salvador, Bahia, have been reported since ProAR's intervention (14).

Design

This was a cross-sectional study of 508 patients, of both genders and above 18 years of age, diagnosed with severe asthma at the moment of enrolment in the program, and patients participated in ProAR for at least 6 months. According to the GINA criteria, severe asthma was characterized by continuous asthma symptoms, limitations to physical activities, frequent exacerbations, night awakenings, the need for the daily use of a bronchodilator, and low forced expiratory volume in 1 second (FEV₁) on spirometry (6). Patients regularly seen for medical outpatient consultations, capable of correctly performing the inhalation of prescribed medications, and presenting satisfactory adherence to treatment were considered eligible to participate in the study (15). Exclusion criteria included the diagnosis of pulmonary disease other than asthma, abnormal chest X-ray, and smoking more than 10 packs of cigarette/year.

All the participants answered a sociodemographic (including variables such as age, gender, ethnicity, educational level, and family income) and a clinical questionnaire of asthma-related (including information such as emergency visits, hospitalization, and corticosteroid use), allergic rhinitis, gastro-esophageal reflux disease

(GERD), and other comorbidity questions. Moreover, participants completed the Asthma Control Questionnaire (ACQ) (17) and performed a standard pulmonary function 130 test (16) every 6 months.

Asthma Control

The control of asthma was assessed by the shortened version of the ACQ (17) that was validated for use in adult outpatients in Brazil (18). This questionnaire comprises six questions: five of these refer to asthma symptoms or limitations (nocturnal symptoms, morning symptoms, limitations to daily activities, dyspnea, and wheezing), and one question is related to the use of rescue β_2 -agonist medication (17). Each item score ranges from 0 (well controlled) to 6 (extremely poorly controlled), and according to a previously published study, results >1.5 indicated lack of asthma control (18).

Obesity

Height, weight, and waist and hip circumferences were measured, and the body mass index (BMI) was calculated. BMI was defined as the weight in kilograms divided by the square of the height in meters. According to the International Standard Definition (19), BMI <25 kg/m² was classified as normal, $30 > \text{BMI} \geq 25$ kg/m² was classified as overweight, and BMI ≥ 30 kg/m² was classified as obese. Obesity was further subdivided into three classes according to the National Heart, Lung, and Blood Institute obesity classification (20): class I ($30 \leq \text{BMI} \leq 34.9$ kg/m²), class II ($35 \leq \text{BMI} \leq 39.9$ kg/m²), and class III (BMI ≥ 40 kg/m²).

Pulmonary Function Tests

Trained technicians conducted spirometry test maneuvers on the day of the clinic visit. Standardized maneuvers were performed according to the American Thoracic Society guidelines (16). The percentage of predicted FEV₁ was calculated using reference values for the Brazilian population (21).

Statistical Analysis

Descriptive analysis was used on the frequencies of occurrence, measures of central tendency, and statistical dispersion. Univariate analysis was performed with chi-square test and Fisher's exact test. Multivariate logistic regression included factors with a p -value $\leq .10$. Each variable was adjusted to those found to be predictors for uncontrolled asthma.

The results are presented as odds ratio (OR) with a 95% confidence interval (95% CI). Two-tailed tests were carried out and p -values $< .05$ were considered statistically significant. The database was analyzed using the Statistical Package for the Social Sciences, v. 14.0 (SPSS, Chicago, IL, USA).

Ethical Aspects

The Ethics Committee of the Federal University of Bahia (IRB approval number: 4123) approved this study, and

all the participants signed terms of informed consent. All patients enrolled in the program were informed about the research purposes and anonymity.

RESULTS

Sample Characteristics

This study enrolled 508 patients with severe asthma who were followed up at the central reference clinic of ProAR. Sociodemographic characteristics and comorbid medical conditions are presented in Table 1. The majority of the participants were women (79.3%) and Afro-descendants (88.4%) with a mean age of 50.57 ± 13.80 years, and the mean age at the onset of asthma symptoms was 18.21 ± 17.09 years. The mean BMI for the sample was 28.03 ± 5.88 . The patients were classified as follows: 17.9% of patients in obesity class I, 10.3% in obesity class II, and 3.7% in obesity class III.

Approximately two-thirds of the patients reported less than a high school education and 64% had an income of less than 500 US dollars per month. In addition, 92.3% of patients had symptoms of chronic rhinitis, 47.6% presented with GERD, and 28.7% were current or former smokers. Only two patients (0.4%) reported regular use of oral corticosteroids, whereas 36.8% visited an emergency room and 3.2% had a previous hospitalization in the past year due to their asthma. Lung function tests detected a FEV₁ (% predicted) mean of $62.16 \pm 19.18\%$ and a mean FEV₁/FVC of $76.14 \pm 15.25\%$.

TABLE 1.—Table characteristics and comorbidities of 508 subjects with severe asthma.

Variable	N (%)
Female (%)	403 (79.3)
Black (%)	449 (88.4)
Age (years), mean $\pm$ SD	50.57 ± 13.80
Onset age of asthma symptoms, mean $\pm$ SD	18.21 ± 17.09
BMI (kg/m ²), mean $\pm$ SD	28.03 ± 5.88
BMI category frequencies	
BMI 30–34.9 (obesity class I)	91 (17.9)
BMI 35–39.9 (obesity class II)	52 (10.3)
BMI ≥ 40 (obesity class III)	19 (3.7)
Education	
<High school	312 (61.4)
$\geq$ High school	194 (38.1)
Mensual family income, US\$	
<500	325 (64.1)
≥ 500	182 (35.9)
Comorbidities	
Allergic rhinitis	469 (92.3)
GERD	242 (47.6)
Hypertension	210 (41.3)
Diabetes	45 (8.9)
Current or former smokers	146 (28.7)
Oral corticosteroids use (past 12 months)	2 (0.4)
Emergency visits (past 12 months)	187 (36.8)
Previous hospitalization (past 12 months)	16 (3.2)
Spirometry, mean $\pm$ SD	
FEV ₁ (% of predict)	62.16 ± 19.18
FEV ₁ /FVC (%)	76.14 ± 15.25

There was a high occurrence of overweight participants (the average BMI was 28.03 kg/m^2 and the range was 16.8 ± 52.0), and only 33.7% of participants were classified as normal weight, compared with 34.4% and 31.9% classified as overweight and obese, respectively.

Effect of Obesity on Asthma Control

In the population analyzed, the ACQ score had a median of 1.0 and the interquartile range was 1.67. Asthma control scores were dichotomized into controlled and uncontrolled asthma (ACQ > 1.5). According to this parameter, 59.3% of the subjects had controlled asthma, whereas 40.7% of subjects had uncontrolled asthma.

Linear regression demonstrated a positive association between BMI and lack of asthma control (OR 1.5; 95% CI 1.02–2.20) (Table 2). Symptoms of chronic rhinitis and GERD were also significantly associated with uncontrolled asthma (OR 3.68, 95% CI 1.50–9.01; and OR 2.78, 95% CI 1.91–4.03, respectively). There was no association between waist-to-hip ratios and asthma control.

These associations remained in the logistic regression analysis after adjustment for age, gender, ethnicity, income, smoking status, and duration of asthma treatment. Obese subjects with severe asthma were more likely to have uncontrolled asthma than patients with a BMI $\leq 30 \text{ kg/m}^2$ (OR 1.6; 95% CI 1.05–2.46) (Table 3). We also found that obese patients who also had GERD were at higher risk for uncontrolled asthma (OR 2.97; 95% CI 1.55–5.67). This finding demonstrates that the presence of GERD in obese patients has a significant and negative impact on asthma control. Individuals with normal BMI, when compared to other patients, had an OR of 0.97 for uncontrolled asthma (95% CI 0.661–1.42). Overweight patients had a 0.64 times chance of having uncontrolled asthma when compared to other participants (95% CI 0.43–0.93), whereas those considered obese had an OR of 1.50 (95% CI 1.02–2.20).

The relationship between asthma control and the different classes of obesity was also investigated. Asthmatics

TABLE 2.—Predictors of lack of control among 508 subjects with severe asthma, by univariate logistic regression.

Variables	OR	95% CI
Age (years)	0.99	(0.98–1.01)
Female	0.97	(0.62–1.15)
Black	0.85	(0.49–1.48)
Mensual income <US\$ 500	1.39	(0.95–2.03)
Arterial systemic hypertension	1.11	(0.77–1.60)
Diabetes	1.17	(0.62–2.19)
Allergic rhinitis	3.68	(1.50–9.01)
GERD	2.78	(1.91–4.03)
BMI $> 30 \text{ kg/m}^2$	1.50	(1.02–2.20)
Mean waist-to-hip ratio	2.18	(0.27–17.5)
Oral corticosteroids	1.52	(0.09–24.4)
Regular ICS use (years)	1.09	(1.01–1.18)
Current or former smokers	1.84	(1.24–2.73)
Mean FEV ₁ (% predicted)	0.99	(0.98–1.00)
Mean FVC (% predicted)	0.99	(0.98–1.00)
Mean FEV ₁ /FVC (% predicted)	0.99	(0.97–1.00)

TABLE 3.—Independent predictors of uncontrolled disease of 508 patients with severe asthma by multivariate logistic regression.

Variables	OR	95% CI
Age (years)	0.99	0.97–1.00
Female	0.79	0.47–1.33
Black	0.87	0.48–1.59
Mensual family income <US\$ 500	1.55	1.02–2.36
Allergic rhinitis	2.97	1.16–7.59
GERD	2.67	1.79–3.96
BMI >30 kg/m ²	1.60	1.05–2.46
Current or former smokers	2.06	1.31–3.23
Regular ICS use (years)	1.09	1.00–1.18

classified in obesity class I, compared to other patients, had an OR for having uncontrolled asthma of 1.15 (95% CI 0.73–1.81). Obesity class II patients had a risk of uncontrolled asthma of 1.28 (95% CI 0.72–2.28), whereas obesity class III patients had a risk of uncontrolled asthma of 3.30 (95% CI 1.23–8.82). Poor asthma control was observed with statistical significance only in the obesity class III subgroup.

DISCUSSION

The results of this study show a higher frequency of both being overweight and obese among severe asthmatics than would be expected for the Brazilian adult population (22). Furthermore, we found a significant association between obesity, symptoms of chronic rhinitis and GERD, and smoking, either at present or in the past, and uncontrolled asthma. To our knowledge, this is the first report on the association between obesity and lack of control on severe asthma in a homogeneous, unicenter sample of patients with regular follow-up care and adherence to proper treatment that is large enough to allow for robust inferences.

These findings are consistent with various other studies on obesity and asthma. The link between obesity and asthma appears to be strong, even if definitive proof of causality is still lacking (23–25). A cross-sectional study of 382 adult patients, designed by Lavoie et al. (26), demonstrated that patients with higher BMIs had higher scores on the ACQ, independent of age, gender, and asthma severity, which indicates that obesity is associated with a decline in asthma control. Likewise, in a prospective study, Saint-Pierre et al. (27) found that a BMI >25 kg/m² reduced the probability of a transition from an unacceptable to an acceptable asthma control state. These authors concluded that compared with nonobese patients, overweight and obese asthmatics were more likely to have poorly controlled asthma despite treatment. Other studies reiterate that obese individuals with persistent asthma are significantly more likely to report poor asthma control, poor asthma-related quality of life, and more asthma-related hospitalizations than those with a normal BMI (28). In addition, there is evidence that weight loss in obese patients with asthma contributes to a

reduction in asthma symptoms and medication needs and the improvement of asthma control (29–32).

Although several studies that evaluated the relationship between obesity and asthma control have been in agreement about their association, some recent reports have presented evidence against this association, particularly in relation to asthma severity (33–35). A Brazilian study that analyzed a total of 200 patients with asthma in a university hospital clinic was unable to demonstrate a correlation between obesity and asthma severity (34). A prospective US cohort study, with 572 patients, found no association between obesity and chronic asthma severity using several measures, such as history of steroid use, the need for intubations, the number of emergency visits, and hospital admissions (35). Asthma severity and asthma control are distinct concepts and their association with overweight or obese conditions must be interpreted cautiously. It seems plausible to consider that obesity may be associated with uncontrolled asthma, in addition to being associated with the presence of asthma and possibly with asthma severity. A large body of evidence suggests that obesity may influence asthma control. Reports have shown that nearly 75% of emergency room visits for asthma occurred among obese individuals, and studies have shown that obesity predates asthma (36). Obesity may also be a risk factor for airway hyper-responsiveness.

Some mechanical and inflammatory phenomena may explain uncontrolled asthma in obese individuals. Obesity affects the anatomy of both the lungs and the airways (37). Increased abdominal and chest wall mass in obese patients causes lower functional residual capacity. Considering lung volume is a major determinant of airway diameter; it is possible that these changes in residual capacity allow the airways to rest in a more narrow state and smooth airway muscles to further reduce airflow when activated.

Chronic low-level systemic inflammation is present in obese patients. The inflammation appears to originate within the adipose tissue, which contains leptin, adiponectin, and plasminogen activator inhibitor-1, all of which contribute to airway hyper-responsiveness. Interestingly, even after controlling for the BMI, leptin levels were increased in obese asthmatic children compared to children without asthma. Studies in animals have suggested that leptin may stimulate mast cells and thus magnify airway hyper-responsiveness to allergens (36, 38, 39).

In our study, in agreement with previous reports (40–43), the ratio between the waist and hip circumference was not correlated with poor asthma control. Musaad et al. (44) found that central obesity was associated with asthma, asthma severity, lower lung function, and less atopy among asthmatic subjects. Their observations suggest that the fat distribution in the thoracic-abdominal region could be more specific than the BMI for evaluating the influence of obesity on the respiratory system.

Various studies provide evidence that chronic rhinitis is associated with asthma severity and lack of control over the disease. We found that rhinitis was a strong predictor of uncontrolled asthma in our sample of severe asthmatics.

Previously, we had reported that severity of chronic rhinitis was positively associated with asthma severity and inversely correlated to an index of quality of life, and we concluded that moderate/severe rhinitis was a strong predictor for greater severity of asthma in our sample (45).

Further, we observed that GERD was diagnosed by a physician in 46.7% of subjects with severe asthma and was an independent predictor for uncontrolled disease in our sample. GERD is a risk factor for asthma-related hospitalizations and oral steroid use (46, 47). Asthmatics may be predisposed to GERD development due to a high prevalence of hiatus hernia, autonomic deregulation, and an increased pressure gradient between the abdominal cavity and the thorax that overrides the lower esophageal sphincter pressure barrier. Asthma medications may also potentiate GERD symptoms. In obese asthmatics, an increased abdominal pressure may intensify GERD and contribute to persistent asthma symptoms (48).

This study has some potential limitations that should be noted. First, only patients with severe asthma were enrolled in the study; therefore, our findings cannot be extrapolated as valid for individuals with mild/moderate asthma. However, our goal was to study the association between obesity and asthma control in severe asthma cases, and we have done so with a powerful sample. Second, the study design itself does not allow inferences of causality, which should be addressed in prospective studies.

Several biological mechanisms have been proposed to explain the influence of obesity on asthma (49, 50). Meticulously controlled observational and experimental studies are required to better understand the relationship between obesity and asthma outcomes, and they lead to improved strategies for the treatment of this specific group of patients.

Our results reinforce the positive association between obesity and lack of asthma control and have important implications for clinical practice, as subjects with severe asthma and obesity may be more difficult to control. Perhaps a treatment strategy, including controller medication for asthma combined with major efforts toward a healthy diet and proper physical activity, will bring better results than the usual narrow reliance on drugs.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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