

Obesity-asthma phenotype: Effect of weight gain on asthma control in adults

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ABSTRACT

Introduction: The obesity-asthma phenotype has become an increasingly common situation in our clinical practice. The mechanisms behind poor asthma control in subjects who are obese remain unclear. We aimed to determine the effect of obesity on asthma control in a group of adult patients

Method: Subjects who had been diagnosed as having asthma and who were admitted to our clinic were included to this study. Body mass index (BMI) and asthma control status of the patients were evaluated. BMI values at the time of diagnosis were also collected from the patient files, and the difference between basal and current BMI values were calculated. The effect of obesity and weight gain on asthma control was investigated.

Results: The study population was composed of 218 patients (29 men, 189 women), with a mean (standard deviation) age of 52.01 ± 11.6 years. Fifty-four percent of the patients were obese, 27.5% were overweight, and 18.3% were of normal weight. The baseline and current BMI values were higher in women than in the men. BMI increased with the increase in age or disease duration. Asthma control was poor in the patients who were obese and overweight despite optimal treatment. Moreover, asthma control was worse in patients who gained weight during the follow-up period.

Conclusion: In our study, we found a significant relationship between obesity and asthma control. In addition, weight gain and being nonatopic also was found to worsen asthma control. In light of our finding that weight gain led to a decrease in asthma control, we suggest that weight loss may improve the course of asthma.

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Obesity and asthma are important chronic multifactorial health problems, and the prevalence of both are increasing worldwide.^{1–3} Obesity and being overweight are associated with a number of health hazards including diabetes, hypertension, cardiovascular disease, and respiratory problems (e.g., obstructive sleep apnea).^{3,4} Furthermore, evidence from recent years indicates that obesity is a major risk factor for the development of asthma.^{3,5}

Although asthma may promote weight gain because of an increased sedentary lifestyle and the adverse effects of corticosteroid use, obesity precedes asthma in the vast majority of subjects.⁶ Various mechanisms have been proposed to explain how obesity could trigger asthma development, such as the influence of lung mechanic, influence of obesity-associated systemic inflammation, increased prevalence of asthma-related comorbidities, and genetic and environmental factors.³

The obesity-asthma phenotype has become an increasingly common situation in our clinical practice.

Asthma in patients who are obese is often characterized as severe, poorly controlled, and less responsive to asthma treatment.⁷ Moreover, early morning symptoms, dyspnea and wheezing, nighttime awakening, and limitation of daily activities are more prevalent and persistent in patients with asthma and who are obese.² The mechanisms behind poor asthma control remain unclear. The number of patients with obesity-asthma phenotype and who are followed up in our clinic has increased day by day. We aimed to investigate the effect of obesity on asthma control in a group of adult patients.

METHOD

This was a retrospective case-control study. Six hundred and fifty patients with a diagnosis of asthma who had been admitted to our outpatient clinic between September 2012 and March 2013 were screened. The subjects who had complete file records since the first admission were included in the study. An asthma diagnosis was based on a history of recurrent symptoms of wheezing, shortness of breath, and cough, and demonstration of objective signs of reversible airway obstruction by means of a >12% increase in forced expiratory volume in 1 second (FEV₁) after 15 minutes with an inhalation of 200 mg of salbutamol by positive methacholine bronchial provocation test by means of at least a 20% decrease in FEV₁ with a methacholine dose of ≤ 8 mg/mL according to the recommendations of

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the Global Initiative for Asthma guidelines.⁸ Those patients followed up at least 1 year with complete BMI records at the time of diagnosis were invited to participate in the study ($n = 250$). Two hundred and eighteen patients agreed to participate in the study and were enrolled. The patients were evaluated for demographic characteristics, family histories, BMI, disease characteristics, pulmonary function tests, asthma control status, and comorbid diseases.

The patients' weight and height were measured, and BMIs were calculated. BMI values were classified as follows: 18–24.9 kg/m², normal; 25–29.9 kg/m², overweight; 30–34.9 kg/m², class-1 obese; 35–39.9 kg/m², class-2 obese; >40 kg/m², class-3 obese. The patients were classified according to their BMI values both at diagnosis and in the current evaluation as described above. Because the interval time was not the same for all the subjects, we selected a group of patients for whom the interval time was between 6 and 10 years. The difference between baseline and current BMI were calculated, and the relationship between change in BMI and other variables were evaluated in this group. By using this method, the effect of either obesity or weight gain on the asthma control status was evaluated.

The asthma control test (ACT) was used with all the patients at the last evaluation.⁹ An ACT score of 25 indicated that asthma was totally controlled, 20–24 indicated asthma to be partially controlled, and <20 meant that asthma was uncontrolled. For the totally controlled group, the patients who had no asthma symptoms and had not required asthma treatment for at least 2 years were classified as in remission.

Current and past asthma medication use was investigated by the use of file records as dose of the medication, dose escalations or reductions, inhalation technique, and drug consumption according to patient statement recorded at each visit. The patients' atopy status was examined either with skin-prick tests or specific immunoglobulin E measurements. For prick test allergen extracts (Allergopharma, Reinbek, Germany) along with appropriate positive (histamine 10 mg/mL) and negative (saline solution) controls were applied on the forearm by using the prick technique. Prick test response to common aeroallergens: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, a mixture of grass pollens, a mixture of weed pollens, a mixture of tree pollens, a mixture of cereal pollens, a mixture of molds, and animal epithelia was investigated. The skin test results were read after 15 minutes, and a wheal size of ≥ 3 mm was considered positive. Specific immunoglobulin E measurements were performed by CAP fluoroenzyme immunoassay (Phadia, Uppsala, Sweden) according to recommendation of the manufacturer.

The study group was questioned for allergic diseases, such as allergic rhinitis, nasal polyposis, urti-

caria, angioedema, and drug or venom allergy. They also were asked about the presence of systemic diseases, such as obstructive sleep apnea syndrome, gastroesophageal reflux disease, diabetes mellitus, hypertension, and cardiovascular diseases. Physical examination and pulmonary function tests were undertaken. Pulmonary function tests (FEV₁, forced vital capacity, peak expiratory flow, and maximum midexpiratory flow) were performed by using a spirometry device (ZAN 100, Würzburg, Germany) and evaluated in accordance with the American Thoracic Society/European Respiratory Society guidelines.¹⁰ The study was approved by the medical ethics committee of Ankara University School of Medicine. Written informed consent was obtained from all the participants.

Statistical Analysis

The statistical analysis was performed by using SPSS version 20.0 (SPSS Inc., Chicago, IL). Numeric values with normal dispersion were expressed as means (standard deviation), whereas abnormally dispersed variables were given as median (minimum-maximum). Categorical variables values were given as number (%). The χ^2 test was used for comparison of two independent groups for categorical data. The Student's *t*-test was used to compare the two normally dispersed groups. The importance of the difference according to the means among the groups was examined with analysis of variance. The Mann-Whitney *U* test or Kruskal-Wallis test was used to determine the importance of the difference in medians among the independent groups, and the Wilcoxon signed rank test was used in related samples. All directional *p* values were two-tailed, and significance was assigned to values of <0.05.

RESULTS

A total of 218 patients (29 men, 189 women) with a mean (standard deviation) age of 52.01 ± 11.6 years were enrolled into the study. The median disease duration of the patients was 13 years (minimum-maximum, 1–50 years). Disease duration was >10 years in 67.4% of the patients. With regard to periodic visits, 72% of the patients had routine follow-up visits every 3 months, whereas the remaining 28% had at least one visit per year. Comorbid diseases were present in 78.9% of the patients, including allergic comorbid diseases (70.9%) and systemic comorbidities (70.3%). The atopy ratio was 48.6% in our study population. Leading sensitizations were pollens (32% [$n = 34$]), mites (28.3% [$n = 30$]), molds (7.5% [$n = 8$]), and pets (3.7% [$n = 4$]).

When the patients were evaluated according to BMI values, 54.1% were found to be obese (class 1 obese, 36.2%; class 2 obese, 10.1%; class 3 obese, 7.8%), 27.5% were considered to be overweight, and 18.3% were of

Table 1 Patient demographic characteristics

	Normal Overweight		Obese Class			Total	p
			1	2	3		
Sex, no. (%)							0.003
Men	9 (22)	14 (23)	6 (8)	0	0	29 (13)	
Women	31 (78)	46 (77)	73 (92)	22 (100)	17 (100)	189 (87)	
Age, no. (%)							0.002
18–35 y	10 (25)	5 (8)	2 (3)	0	1 (6)	18 (8)	
36–50 y	12 (30)	20 (33)	31 (39)	3 (14)	8 (47)	74 (34)	
51–65 y	14 (35)	25 (42)	40 (51)	14 (64)	6 (35)	99 (45)	
>65 y	4 (10)	10 (17)	6 (7)	5 (23)	2 (12)	27 (12)	
Age of disease onset, no. (%)							0.06
≤40 y	28 (70)	30 (50)	40 (51)	10 (45.5)	13 (76.5)	121 (56)	
>40 y	12 (30)	30 (50)	39 (49)	12 (54.5)	4 (23.5)	97 (45)	
Asthma duration, median (minimum-maximum), y	10 (1–35)	12 (1–38)	15 (1–41)	15.5 (3–37)	15 (2–50)	13 (1–50)	0.05
Atopy, no. (%)	23 (22)	30 (28)	34 (32)	12 (11)	7 (7)	106 (49)	0.56
Comorbidity (n = 172 [78.9%]), no. (%)							0.73
Allergic diseases (n = 122 [70.9%])							
AR	14 (64)	14 (42)	22 (47)	6 (46)	1 (15)	57 (46)	
AR + other allergic diseases	5 (23)	13 (39)	13 (28)	3 (23)	2 (28)	36 (30)	
Without AR	3 (14)	6 (18)	12 (25)	4 (31)	4 (57)	29 (24)	
Systemic diseases (n = 121 [70.3%])							
GERD	0	7 (22)	9 (19)	3 (16)	3 (21)	23 (19)	0.17
OSAS	0	0	0	0	3 (21)	3 (3)	0.00
DM	2 (22)	6 (18)	19 (40)	4 (21)	6 (43)	37 (31)	0.01
HT	3 (33)	14 (44)	28 (60)	13 (68)	7 (50)	62 (53)	0.00
Asthma control status, no. (%)							0.17
Uncontrolled	8 (14)	14 (24)	19 (32)	9 (15)	9 (15)	59 (27)	
Partially controlled	16 (23)	18 (25)	27 (38)	5 (7)	5 (7)	71 (33)	
Totally controlled	16 (18)	28 (32)	33 (37)	8 (9)	3 (3)	88 (40)	
Remission*	6 (38)	3 (11)	6 (18)	1 (12)	0	16 (18.1)	

AR = allergic rhinitis; GERD = gastroesophageal reflux disease; OSAS = obstructive sleep apnea syndrome; DM = diabetes mellitus; HT = hypertension.

*For the whole study group, 7.3%.

normal weight (Table 1). The BMI values of the women were higher than those of the men both at diagnosis and at current examination time. The patients' BMI increased with the increase in age or disease duration ($p < 0.05$). The patients who were between 18 and 35 years old had significantly lower BMI values than did the older patients, both at diagnosis and at the last evaluation ($p = 0.001$). Moreover, patients whose disease duration was <5 years were leaner than those who had had asthma for >10 years ($p = 0.01$). We found no significant difference between BMI values and atopy, and age of disease onset.

When we classified patients according to their asthma control status: 27.1% had uncontrolled, 32.6% had partially controlled, and 40.4% had totally controlled asthma. When the patients in the totally controlled group were evaluated for remission state, 18.1% were in remission, and this ratio was 7.3% for the whole study population. The latest BMI values were significantly higher in the uncontrolled group than in the partially and totally controlled groups ($p = 0.03$) (Figure 1), but there were no differences in baseline BMI values among the groups. The median (minimum-maximum) BMI values of the whole group was 30

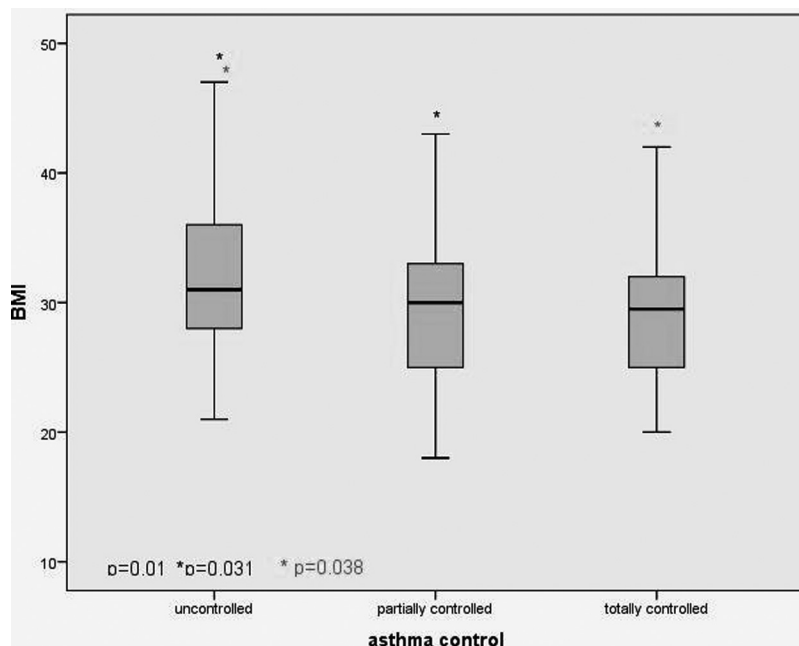


Figure 1. Relationship between body mass index (BMI) and asthma control status.

kg/m² (18–47 kg/m²) at the last examination and 28 kg/m² (17–46 kg/m²) at the time of diagnosis ($p < 0.001$).

In the follow-up, a change in BMI and its relationship with variables such as age, sex, disease duration, and asthma control, were evaluated in a group of patients ($n = 93$) in whom the interval between records was 6–10 years. Fifty-six percent (52/93) of the patients' BMI values were increased, 14% (13/93) were unchanged, and 30% (28/93) had decreased. There was no relationship between the BMI value change in years and the patient age, sex, and disease duration. When patients were classified according to their control status, the median BMI value had increased during the evaluation period and the difference between the BMI value at baseline and the last evaluation was significant in all the groups except the remission group ($p < 0.001$). The ratio of the patients whose BMI value had increased during the evaluation period was the highest in the uncontrolled group (73.1%), it was 64.3% in the partially controlled group, 43.8% in the totally controlled group, and 14% in the remission group ($p = 0.04$) (Figure 2). Furthermore, more than half of the patients in remission and 43.8% of the patients in the totally controlled group had an unchanged BMI value.

There was no relationship between the patients' treatments, including long acting β -adrenergic bronchodilator, inhaler corticosteroid, or leukotriene receptor antagonists, and BMI values both at diagnosis and the last evaluation. However, the patients who were receiving an oral corticosteroid regimen ($n = 15$) were more obese than the others both at diagnosis ($p = 0.01$)

and at the last evaluation ($p = 0.005$). In the follow-up group ($n = 93$; interval period, 6–10 years), there were no patients who received oral corticosteroid. The atopy ratio was lower in patients who were obese (45% [53/118]) than in those who were of normal weight (57.5% [23/40]). Asthma control was better in patients with atopy. The rates of totally controlled asthma were 48.1% and 33% in atopic and nonatopic groups, respectively. Moreover, patients who were obese and atopic had better disease control than those who were obese but nonatopic; 49.1% ($n = 26$) of the patients who were obese and atopic had totally controlled asthma; however, this ratio in patients who were nonatopic and obese was 27.7% ($n = 18$) ($p = 0.05$).

Asthma began before reaching 40 years of age in 70% of the patients with atopy. In patients without atopy, this ratio was 40% ($p < 0.001$). When patients were evaluated according to their BMI classifications, asthma began earlier in patients with atopy in all of the weight categories ($p < 0.01$). Asthma began after reaching 40 years of age in more than half of the patients who were obese but nonatopic ($p = 0.01$).

When the pulmonary function tests were evaluated in relation to the patients' obesity groups, the mean values of FEV₁, forced vital capacity, and maximum midexpiratory flow were 82.4, 95.9, and 54%, respectively, in the patients of normal weight; 80.3, 91.8, and 54.9%, respectively, in those who were overweight; 83.8, 91.6, and 55%, respectively, in class 1 obese; 84.8, 91.2, and 56.2%, respectively, in class 2 obese; and 72.7, 87, and 41%, respectively, in class 3 obese. We found no significant relationship among FEV₁, forced vital capacity, maximum midexpiratory flow values, and obesity groups.

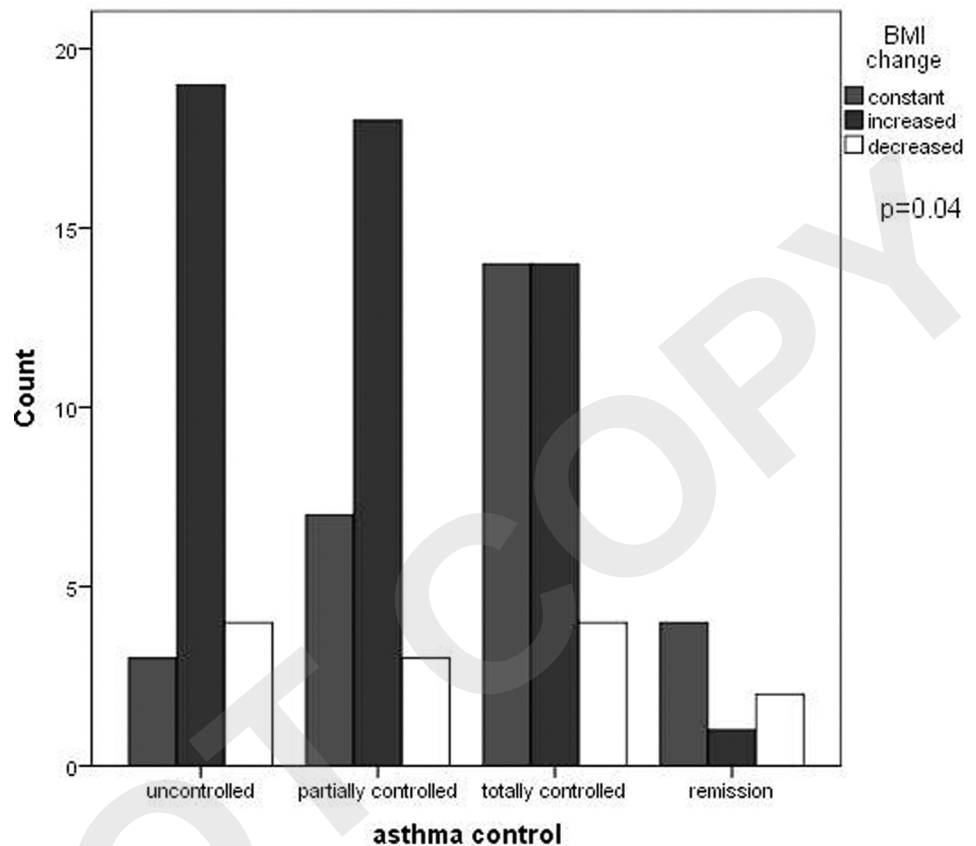


Figure 2. Body mass index (BMI) change for asthma control groups ($n = 93$).

DISCUSSION

Asthma is a heterogeneous disease constituted by separate overlapping syndromes and, as such, there is a need to identify each group of patients.¹¹ In 2010, the American Thoracic Society workshop concluded that asthma in patients who are obese may represent a unique phenotype. There are several previously identified phenotypes gathered under five main headings, depending on the clinical specialities, triggers, inflammation type, molecular phenotypes, and others.¹² Altered lung mechanics, a high fat diet, genetic pleiotropy, comorbidities, asystemic or airway inflammation, and oxidative stress were thought to be the responsible factors for the development of the obese-asthma phenotype.^{13,14} In addition, obesity decreases chest wall compliance, which results in reduced lung volumes, increased work of breathing, and increased energy and oxygen costs of breathing. As a result of this mechanism, patients who are obese report more dyspnea and asthma-like symptoms than patients who are not obese; they may be more likely to be misdiagnosed by their physician as having asthma. Aaron *et al.*¹⁵ drew attention to the increased risk of overdiagnosed asthma in patients who are obese.

We know that in the obese phenotype; asthma course is poor, reliever medication necessity increases, quality of life is bad, and the response to controller medication

is variable.¹⁶ However, the underlying mechanism is still not clear. Most of the studies in the literature about the obesity-asthma phenotype demonstrated that there was a significant association between asthma control and obesity. Many researchers reported a linear relationship between asthma severity and obesity, and concluded that patients with asthma who were obese had worse asthma control.^{17–19} Some researchers only found this relation in female patients.^{20,21} However, no relationship was reported between obesity and asthma control in some studies.^{22–24} The reason for these contradictory results may be due to the differences in measures of asthma control or characteristics of study cohorts.² In our study, we found a significant relationship among obesity, weight gain, and asthma control. Patients with uncontrolled asthma had higher BMI values than had the patients who had partially and totally controlled asthma. In accordance with previous studies,^{20,21} we found a significant relationship in women but not in men; however, this was attributed to the predominance of females in our study group.

In general, our study group gained weight over the years, independent of sex, age, and disease duration. In addition, an increase in body weight yielded to worsening of asthma control. In asthma, obesity is associated with reduced sensitivity to glucocorticoids, both clinically and *in vitro*.²⁵ This raises a question as to

whether patients gain weight secondary to the corticosteroid regimen that is implemented due to uncontrolled asthma or whether obesity deteriorates asthma control. Although both conditions are possible, it is hard to make a comment on this situation because there were no patients who were receiving oral corticosteroid in the group we analyzed for the change in BMI index. A previous meta-analysis showed that weight gain almost doubled the odds of the incidence of asthma.²⁶ Shore²⁷ documented that a weight gain of >25 kg gave a fourfold increase to the relative risk of asthma. Most of the studies in the literature showed significant improvement in asthma control and severity with weight loss.^{26,28} We also suggest that clinicians should consider BMI in all asthma cases in light of these findings.

The relationship of asthma and obesity with atopy has also been investigated in some studies,²⁹ and a strong link between obesity and asthma was found in individuals without atopy.^{1,30} Several studies revealed that patients who were obese and nonatopic had an increased risk of asthma when compared with those who were atopic.^{29,31} Two distinct phenotypes of obese asthma were described: one type was early onset atopic asthma, complicated by obesity, and the second was late-onset nonatopic asthma, which is caused by obesity.³² In our study, atopy was less frequent in patients who were obese and with asthma, albeit not significant, which was similar to the literature. Furthermore, we found better asthma control in patients who were obese and atopic than those who were obese but nonatopic. This can be explained based on the reports that there is a lack of eosinophilic inflammation that results in a variable response to controller medication in patients who are obese and with asthma when compared with subjects with normal weight and with asthma.^{33,34} To our knowledge, this is the first study to demonstrate the relationship of atopy and asthma control in patients who are obese. When our results were taken together, we could hypothesize that our study group also included two phenotypes of obese asthma with early onset atopic asthma, complicated by obesity, and the second type with late-onset nonatopic asthma, which was caused by obesity. These findings revealed the importance of encouraging weight loss and preventing obesity in patients who are obese and nonatopic to achieve better asthma control.

Several limitations of the study may be highlighted. We confirmed that most of these limitations were due to the partially retrospective design of the study and the small patient group from a single center. The most notable limitation was the lack of baseline asthma control evaluation. Baseline ACT data would help us to make a stronger conclusion about the effect of weight gain on asthma control status. Due to the partially retrospective design of the study, we did not establish

baseline ACT data for the entire group. Another limitation of the study was the inhomogeneous distribution of sexes because women were predominant in the study group. When the outpatient file records of the past 10 years were investigated, we saw that women comprised the majority of patients with asthma, and we realized that they also came to their follow-up visits more regularly than did the men. As we explained in the Methods section, one of the patient selection criteria was having complete follow-up records, and this criterion was predominantly met by the female patients. Also, the effect of comorbidities such as rhinitis and gastroesophageal reflux disease on asthma control could give additional information for discussion; however, the number of patients with comorbidities in each group was too low to make such a subgroup analysis.

CONCLUSION

We found a relationship between obesity and asthma control. In addition, patients with weight gain and without atopy had the worst asthma control in our study group. In light of these finding, we believe that BMI should be considered in all patients with asthma and to encourage weight loss in patients who are obese and patients who are overweight.

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