



Effect of Obesity on Pulmonary Function in Children with Mild Persistent Asthma

Hafif Persistan Astımlı Çocuklarda Obezitenin Solunum Fonksiyonları Üzerine Etkisi

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ABSTRACT

Objective: The prevalence of asthma is increased in obese individuals. There is no concrete evidence that an increase in body mass index is associated with a loss of pulmonary function in childhood asthma. Our aim was to investigate the effect of obesity, atopy, and sex on pulmonary function in asthmatic children.

Materials and Methods: This study is a cross-sectional analysis in children with mild persistent asthma. A total of 76 obese and 55 lean children with asthma were recruited. All of the participants were assessed by pulmonary function tests. Skin prick tests including common aeroallergens were performed to all patients.

Results: No differences were found in pulmonary function test parameters between obese and lean patients with asthma. In obese patients with asthma, the ratio of forced expiratory volume in 1 s to forced vital capacity (FEV1/FVC) was significantly lower in nonatopic (92.1±6.4) than in atopic patients (95.5±5.3, p=0.02). We also demonstrated that FEV1/FVC was significantly lower in nonatopic obese patients (92.1±6.4) than in nonatopic lean patients with asthma (95.6±4.7, p=0.05).

Conclusion: Obesity does not seem to be affecting pulmonary function in children with well-controlled mild persistent asthma. However, airways of nonatopic obese asthmatics are negatively affected.

Key words: Asthma, atopy, body mass index, obese, respiratory function

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ÖZ

Giriş: Obez bireylerde astım prevalansı artmıştır. Çocukluk astımında vücut kitle indeksindeki artışın solunum fonksiyonlarını kötüleştirdiğini gösteren kesin kanıt yoktur. Amacımız astımlı çocuklarda obezite, atopi ve cinsiyetin solunum fonksiyonu üzerine etkisini araştırmaktır.

Gereç ve Yöntem: Çalışma hafif persistan astımı olan çocuklarda yapılan kesitsel bir analizdir. 76 obez astım ve 55 normal kilodaki astımlı çocuk çalışmaya alındı. Tüm katılımcılar solunum fonksiyon testi ile değerlendirildi. Tüm hastalara sık saptanan aeroallerjenler ile deri prick testi yapıldı.

Bulgular: Obez ve normal kilodaki astımlı çocukların solunum fonksiyon test parametreleri arasında fark yoktu. Obez astımlı hastalarda atopik olmayanların (92.1±6.4) birinci saniyedeki zorlu ekspiratuvar volümün zorlu vital kapasiteye oranı (FEV1/FVC) atopik (95.5±5.3, p=0.02) olanlara göre daha düşüktü. Aynı zamanda atopik olmayan obezlerin (92.1±6.4) FEV1/FVC oranının atopik olmayan normal kilodaki astımlı çocuklardan (95.6±4.7) daha düşük olduğu saptandı (p=0.05).

Sonuç: Obezitenin iyi kontrollü, hafif persistan astımı olan çocukların solunum fonksiyonunu etkilemediği görülmektedir. Ancak, atopisi olmayan obez astımlı çocukların hava yolları daha fazla etkilenmektedir.

Anahtar kelimeler: Astım, atopi, obezite, solunum fonksiyonu, vücut kitle indeksi

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INTRODUCTION

Asthma and obesity are increasingly prevalent health problems in children and adults (1,2). Cross-sectional and case-control studies in children and adults have demonstrated an increased prevalence of asthma in obese individuals (3-6). Responsible mechanisms include a sedentary lifestyle, dietary factors, reduced chest wall compliance, insulin resistance, comorbidities, and common genetic predisposition (6-8). Since asthma is the chronic inflammatory disease of airways, obesity-induced chronic inflammation has also been implicated in the lung inflammation (9).

Studies show that pulmonary function measurements are required to determine the severity of the asthma and obesity may increase severity of asthma (6,10). FEV1/FVC ratio has been found to have potential relevance in the relationship between BMI and asthma severity (11). Asthma tends to be more severe in overweight and obese children than in normal weight peers (12). A modest association has been reported between elevated BMI and a reduced therapeutic effect of inhaled corticosteroid (ICS)-containing regimens in the mild and moderate persistent asthma population (13).

Many investigators have demonstrated effects of obesity on lung volumes (6). However, there is no concrete evidence that an increase in body mass index (BMI) is associated with a loss of lung function in childhood asthma, besides the usual effects of obesity on lung volume (11,14,15). Normal pulmonary function has been reported in childhood asthmatics with increased BMI (3,6,16,17). On the other hand, FEV1/FVC decline with increasing BMI, indicating that obesity promotes airway obstruction and decline in FVC in adults, but no change with BMI or even increased FVC with BMI in children have been also reported in literature (6).

A specific interaction of obesity and asthma on pulmonary function has not been demonstrated in childhood asthma (11,12,15,18). Relationship between obesity and asthma were found only in females (6). Effects of BMI on the risk of atopy have been examined but the effect of atopy on pulmonary functions in obese asthmatics has not been described (6).

This study aimed to investigate the effect of obesity on pulmonary function in mild persistent asthmatic children and how it is modified by sex and atopic disease.

MATERIALS and METHODS

Study Population

One hundred thirty-one children with physician-diagnosed asthma (67 boys and 64 girls, aged between 6-16 years) from the outpatient clinic of the pediatric allergy unit were enrolled in the study. Patients were categorized into two groups as obese children with asthma (n=76) and lean children with asthma (n=55). We compared the groups according to sex and atopy.

The patients had been previously diagnosed with asthma according to the Global Strategy for Asthma Management and Prevention Classification (GINA) based on a history of intermittent wheezing and demonstration of reversible airway obstruction as defined by at least a 12% improvement in forced expiratory volume in 1 s (FEV1) following bronchodilator administration (19). All children had mild persistent, well-controlled asthma at the time of evaluation and had been using inhaled corticosteroids of either 200 µg fluticasone propionate or 400 µg budesonide. Asthma control status was determined according to GINA guidelines (19). Children with a history of attacks requiring systemic corticosteroids within 3 months and having inhaled β_2 agonist at the day of pulmonary function test were excluded from the study.

All of the participants were assessed by a physical examination. Each patient's height was measured with a standard wall-mounted stadiometer. Weight was measured with a calibrated electronic scale. BMI was calculated using the weight/height² (kg/m²) formula. Children with a BMI above the 95th percentile for age and sex were defined as obese (as defined by the National Center for Health Statistics, www.cdc.gov). Relative BMI (relBMI) was calculated using the following formula: patient's BMI \times 100/50th percentile BMI for the patient's age and sex (20). Children with a relBMI \geq 120 were defined as obese and children with a relBMI <110 were defined as lean (20).

Puberty and growth spurt are related with increased BMI and increased volumes that affect pulmonary function. Obese subjects with early-onset asthma (<12 years) are characterized by a higher level of airway obstruction compared with obese subjects with late-onset asthma (>12 years) (21). Since PFT results are affected, we evaluated children younger (pre-pubertal age) and older than 10 years and 12 years.

Complete Blood Count

Two ml of blood was drawn into a tube anticoagulated with ethylenediaminetetraacetic acid and then evaluated with a hemocytometer (Abbott Cell-Dyn 3700 system, Abbott Diagnostics, Santa Clara, CA, USA) that was calibrated daily. Total eosinophil count and eosinophil percentages were recorded.

Skin Prick Test

All patients had skin prick tests (SPT) to aeroallergens including *D. farinae*, *D. pteronyssinus*, *Alternaria*, *Cladosporium*, cat, grass mix, weed mix, and tree mix allergens (Stallergenes, France). Negative and positive control for prick tests were also performed. Atopy was defined by a positive skin prick test (SPTs were considered positive if the mean diameter of wheal was ≥ 3 mm) (22).

Pulmonary Function Test

All of the participants were assessed by pulmonary function tests. Pulmonary function tests were performed by using the spirometry (Flowhandy ZAN 100 USB, Germany). The test results including % predicted values of forced vital capacity (FVC), FEV1, the FEV1/FVC ratio, and forced expiratory flow (FEF) at 25-75% were recorded. Immediately prior to testing, patients and their caregivers were provided standardized instructions on the technique of performing forced expiratory maneuvers. An adequate test required a minimum of three acceptable FVC manoeuvres. While performing spirometry, a minimum of three flow-volume loop results were obtained. Acceptable repeatability is achieved when the difference between the largest and the next largest FVC was ≤ 0.150 L and the difference between the largest and next largest FEV1 was ≤ 0.150 L. Efforts were free from artifacts including cough during the first second of exhalation, glottis closure that influences the measurement, early termination or cut-off, leak and obstructed mouthpiece. Duration of 3 seconds exhalation was needed for children. The extrapolated volume was less than 150 mL or 5% of the FVC, whichever was greater (23).

This study was approved by the Institutional Review Board and Ethics Committee. Written informed consent was obtained from each patient and/or their parents.

Statistical Analysis

Data were analyzed using SPSS 17.0 statistical software (SSPS Inc., Chicago, IL, USA). The results of statistical analysis were expressed as the number of observations (n) and mean \pm standard deviation (SD). Shapiro-Wilk's test was used to assess the normality of distribution of the variables, and Levene's test was used to assess the homogeneity of variance among the groups. Comparisons of group means were performed with factorial analysis of variance and Tukey's HSD multiple comparison tests. Correlations between variables were evaluated by Spearman's rho correlation coefficient. The chi-square test was used for comparison of frequencies. A p value < 0.05 was considered statistically significant.

In a one-way ANOVA study, sample sizes of 53, 34, 23, and 22 were obtained from the 4 groups and their means were compared. The total sample of 131 subjects achieves 86% power to detect differences among the means versus the alternative of equal means using an F test with a 0.05 significance level. The size of the variation in the means was represented by their standard deviation which is 1.63. The common standard deviation within a group was assumed to be 5.16.

RESULTS

Obese patients with asthma including 44 boys and 32 girls and lean patients with asthma including 26 boys and 29 girls were participated in the study. The distribution of sex was not significantly different between the groups. Clinical characteristics of children with asthma are shown in Table I. No significant differences were observed in age, duration of disease, atopy, or prior use of inhaled corticosteroids between obese and lean patients with asthma. Allergic rhinitis, family history of asthma and pets at home were more frequent in obese children with asthma (Table I). RelBMI was significantly higher in obese patients than in lean patients with asthma (141 ± 15.8 vs 97.5 ± 7.8 , $p < 0.001$).

No significant differences were found in FEV1, FVC, the FEV1/FVC ratio, and FEF 25-75 values between obese and lean patients with asthma (Table I). We also compared the groups according to sex for mean FEV1, FVC, the FEV1/FVC ratio, and FEF 25-75% and did not find any differences either between or within the groups (Table II). There was no correlation between relBMI and pulmonary function. No correlation was found between relBMI and pulmonary function test parameters for girls or boys.

Table I. Characteristics of obese and lean patients with asthma

	Obese patients with asthma	Lean patients with asthma	p
Patients (n)	76	55	
Age (year)	9.8±2.6	9.5±2.8	0.540
Sex (M/F)	44/32	26/29	0.150
BMI (kg/m ²)	24.5±3.7	16.7±1.7	<0.001
RelBMI	141±15.8	97.5±7.8	<0.001
Duration of asthma (month)	37.3±27.4	27.7±28.3	0.060
Presence of atopy	53 (70)	33 (60)	0.200
Total eosinophil count	312.4±305.3	276.7±301.6	0.510
Eosinophils (%)	4.2±3.6	3.4±2.5	0.180
Allergic rhinitis	46 (60.5)	44 (80)	0.030
Family history of asthma	31 (40.8)	14 (25.5)	0.040
Family history of allergies	50 (65.8)	38 (69,1)	0.420
Passive smoking	16 (21)	8 (14.5)	0.240
Pet at home	8 (10.5)	1 (1.8)	0.050
Pulmonary function test			
FVC %	92.4±14.2	92.3±12.1	0.960
FEV1 %	102.3±14.3	104.4±12.9	0.410
FEV1/FVC	94.5±5.8	96.1±4.4	0.080
FEF 25-75%	107.3±23.2	111.6±25.5	0.310

BMI: Body mass index, relBMI: Relative BMI, FEV1: Forced expiratory volume in 1 second, FEF: Forced expiratory flow, FVC: Forced vital capacity. Values are mean ± SD or number (%) unless otherwise indicated.

Table II. Comparison of pulmonary function test results according to sex

	Obese patients with asthma		p*	Lean patients with asthma		p*	p [†]
	Male	Female		Male	Female		
Patients(n)	44	32		26	29		
BMI	24.9±3.8	24±3.5	0.32	16.5±1.5	16.9±1.8	0.40	<0.001
relBMI	143.1±17.3	138.1±13.3	0.17	97.2±7.2	97.8±8.3	0.76	<0.001
Pulmonary function test							
FVC %	90.3±13.2	95.3±15.2	0.14	89.9±11.9	94.4±12	0.17	0.38
FEV1 %	100.9±14.3	104.3±14.2	0.32	103.3±12.8	105.3±13.2	0.56	0.58
FEV1/FVC	94.5±6.0	94.3±5.5	0.88	96.1±4.5	96.1±4.5	0.99	0.54
FEF25-75%	109.2±25	104.6±20.6	0.40	112.9±24.2	110.5±27.1	0.73	0.53

FEV1: Forced expiratory volume in 1 second, FEF: Forced expiratory flow, FVC: Forced vital capacity.

Values are mean ± SD unless otherwise indicated.

*p= comparison of males and females within the group.

†p= comparison of four groups.

Atopic patients were compared with nonatopic patients to evaluate the effect of atopy on pulmonary function in obese and lean children with asthma. In lean patients with asthma, pulmonary function parameters were not significantly different between atopic and nonatopic patients. However, in obese patients with asthma, the FEV1/FVC ratio was significantly lower in nonatopic than in atopic patients ($p=0.02$). The FEV1/FVC ratio was also significantly lower in nonatopic obese patients with asthma than in nonatopic lean patients with asthma ($p=0.05$). There was no significant difference in the FEV1/FVC ratio between atopic lean and atopic obese patients with asthma (Table III).

In obese patients with asthma, only eight had onset of asthma at ≥ 12 years and 15 patients had onset of asthma at ≥ 10 years. In lean patients, five had onset of asthma at ≥ 12 years and 13 had onset of asthma at ≥ 10 years. There was no correlation between PFT results and duration of disease in obese and lean children with asthma. We also could not find any correlation between PFT results and duration of disease in atopic obese, non atopic obese, atopic lean and nonatopic lean children with asthma. There was negative correlation between duration of asthma and FEF 25-75 in children whose asthma had started < 10 years in both obese and lean asthmatics (Spearman $\rho = -0.28$ and -0.33 , respectively, $p < 0.05$).

DISCUSSION

We investigated the effect of relBMI on pulmonary function in patients with asthma and examined whether the presence of atopy or sex differences affect pulmonary function. In our study, we did not find any differences in FEV1, FVC, FEV1/FVC ratio, and FEF 25-75% between obese and lean subjects with asthma.

A previous study showed that FEV1 and FVC were significantly reduced in overweight/obese children compared with normal weight children (14). Ulger et al. (17) reported that FVC, FEV1, and FEF 25-75% were lower in obese subjects than in nonobese subjects, but the FEV1/FVC ratio was similar. Overall, the discrepancy among these study results can be explained by different ages, degree of asthma severity, control status and/or regular use of inhaled steroid treatment of subjects with asthma. Additionally, this variety could be due to using different BMI cut-off points, BMI z scores or using relBMI for classifying obese children. BMI cut off points that define obesity are not linked to age and do not differ for males or females. BMI varies with age and sex in children. For BMI to be used for grouping or making correlations, it should be compared to a reference-standard that accounts for child age and sex. Consequently, we recommend using relBMI or BMI z scores in children to obtain more accurate results.

Table III. Comparison of the groups according to atopy

	Obese patients with asthma		p*	Lean patients with asthma		p*	p [†]
	Atopic	Nonatopic		Atopic	Nonatopic		
Patients(n)	53	23		33	22		
BMI	24.2±3.3	25.2±4.3	0.290	16.7±1.6	16.8±1.9	0.800	<0.001
relBMI	140.4±15.2	142.2±17.5	0.660	95.4±8.7	100.7±4.8	0.020	<0.001
Pulmonary function test							
FVC %	90.8±13	96.1±16.3	0.140	90.9±12.8	94.2±11.1	0.330	0.380
FEV1 %	101.9±14.2	103.3±14.7	0.710	102.6±13.1	106.7±12.6	0.260	0.580
FEV1/FVC	95.5±5.3	92.1±6.4 ^{††}	0.020	96.4±4.3 [†]	95.6±4.7 [‡]	0.530	0.540
FEF25-75%	109.4±24.3	102.3±20.3	0.230	109.6±24.9	113.4±26.7	0.590	0.530

BMI: Body mass index, **relBMI:** Relative BMI, **FEV1:** Forced expiratory volume in 1 second, **FEF:** Forced expiratory flow, **FVC:** Forced vital capacity.

Values are mean \pm SD unless otherwise indicated.

*p= comparison of atopic and nonatopic patients within the group.

[†]p= comparison of four groups.

^{††}p=0.01, [‡]p=0.05.

Because the FEV1/FVC ratio is commonly used as a measure of the degree of airflow obstruction and severity of asthma, as BMI increases, the FEV1/FVC ratio decreases, leading to more limited airflow (11,24). Davidson et al. (25) demonstrated that obese participants had the lowest FEV1/FVC ratio in children and adolescents. Lang et al. (18) showed that overweight/obese children reported clinically and statistically worse symptoms than those lean participants. Atopy is an important host factor in the development of asthma, and it has been shown that the effect of obesity on asthma is stronger among nonatopic individuals than among those with atopy (26,27). In our study nonatopic obese patients had the lowest FEV1/FVC ratio compared with atopic and nonatopic lean patients with asthma. Moreover, in the nonatopic obese asthma subgroup, an increase in relBMI together with a decrease in FEV1/FVC resulted in more limitation of airflow and airway obstruction. The more severe asthma is, the less response to therapy is expected. Therefore, symptoms of nonatopic obese asthmatic children should be questioned in detail.

Ye et al. (28) concluded that ICS can improve large airway function in normal weight children with asthma. However, ICS has no effect on small airway function and obesity restrains the effect of ICS in children with asthma. We believe that ICS improves airway function mainly in atopic patients and obesity restrains the effect of ICS in only nonatopic patients. Visness et al. (26) identified that obesity was significantly related to current asthma among children and adolescents, and the association was stronger in nonatopic children than in atopic children. In the current study, the FEV1/FVC ratio was significantly lower in nonatopic obese patients with asthma than in atopic obese patients with asthma. Additionally, the FEV1/FVC ratio was significantly lower in nonatopic obese patients than in atopic lean patients with asthma. The presence of atopy appears to result in a higher FEV1/FVC ratio. Since all of the patients were using ICSs, we posit that inhaled steroids may be more effective in obese atopic children with asthma and could lead to a decrease in limitation of airflow. ICS may have a limited effect on pulmonary function in nonatopic obese children with asthma. The lower the FEV1/FVC ratio, the more easily symptoms may be recognized. Symptoms should be more carefully addressed in nonatopic obese asthmatic patients.

Several studies have suggested that obese patients with asthma constitute a specific phenotype of patients

in either early-onset or late-onset (29,30). In our study, most of the patients with asthma had an early-onset phenotype. In the Severe Asthma Research Program study, age at onset of asthma affected the relationship between obesity and asthma (31). Obese subjects with early-onset asthma (<12 years) are characterized by a higher level of airway obstruction and bronchial hyper-responsiveness compared with obese subjects with late-onset asthma (>12 years) (21). In our study, in obese patients, only eight had onset of asthma at ≥ 12 years. The two groups of patients could not be compared because of the small numbers, as well as significant age and BMI/relBMI differences between them.

The relationship between obesity and pulmonary function appears to be affected by sex. Tantisira et al. showed that obesity is associated with limitation of airflow and a reduced FEV1/FVC ratio, mainly in girls (14,11). The incidence and severity of asthma are greater in preadolescent boys, but the relationship between obesity and asthma appears to be more prevalent in girls (32,33). Throughout childhood, girls have a larger airway in relation to lung size than boys, a phenomenon that begins to reverse in adolescence (34). With a particular BMI, girls also have a significantly higher amount of percentage body fat than boys (35). Beydon and Delclaux (21) suggested that a specific relationship between BMI and the FEV1/FVC ratio in girls could be explained by obesity-related earlier puberty and growth spurts, resulting in a higher BMI, increased FEV1 and FVC (FVC was increased more than FEV1), and a lower FEV1/FVC ratio. However, in our study, we did not find these correlations according to sex. In our study, the distribution of age was mainly <10 years and the distribution of fat is different in girls at these ages. Therefore, pulmonary function parameters were not affected. We recommend using relBMI or BMI z scores instead of BMI in asthma studies to prevent bias.

Strengths of our study were using relBMI for comparing obese and lean children with asthma and investigating effect of atopy presence on pulmonary function. Limitations of our study were having small sample size, cross-sectional design and having no correlation with clinical symptoms. Future research with larger sample size is needed to define our results more clearly.

In conclusion, this cross-sectional study showed no differences in pulmonary function test parameters between obese and lean children with well-controlled mild

persistent asthma, suggesting that there is no relationship between relBMI and pulmonary function. However, nonatopic obese children with asthma appear to be most negatively affected indicating that effect of obesity on asthma is stronger among nonatopic individuals and absence of atopy is an important factor for the airway obstruction in obese patients with asthma.

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