

Association between subcutaneous abdominal fat and airway hyperresponsiveness

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ABSTRACT

Epidemiological studies have shown that obesity is significantly associated with airway hyperresponsiveness (AHR). The aim of this study was to determine the effect of abdominal fat distribution on the prevalence of AHR. This study was conducted on subjects who visited the Seoul National University Hospital Gangnam Center from October 2003 to January 2009. Medical records of 3205 subjects who had both a methacholine bronchial provocation test and an abdominal CT scan were retrospectively reviewed. One hundred sixty-one subjects with AHR and their 161 controls were selected for the analysis. Total, subcutaneous, and visceral abdominal fat were objectively measured by an abdominal CT scan. Both body mass index (BMI) and waist circumference were significantly associated with AHR after adjustment for smoking (BMI: OR, 1.20; 95% confidence interval [CI], 1.07–1.35; waist circumference: OR, 1.07; 95% CI, 1.02–1.11). Total and subcutaneous abdominal fat increased the risk of AHR with an OR of 1.47 (95% CI, 1.08–2.02) in the case of total abdominal fat, and an OR of 1.99 (95% CI, 1.19–3.31) in the case of subcutaneous abdominal fat. However, visceral abdominal fat was not associated with AHR. The association between subcutaneous abdominal fat and AHR was consistent, especially in men. Subcutaneous abdominal fat was significantly associated with AHR, but visceral abdominal fat was not. These results suggest a possible role for subcutaneous fat on the later development of asthma.

(Allergy Asthma Proc 32:68–73, 2011; doi: 10.2500/aap.2011.32.3407)

Both obesity and asthma are major health problems in children and adults worldwide. The prevalence of asthma has been increasing in parallel to that of obesity.¹ Asthma is a chronic inflammatory disease of the airway, characterized by reversible airway obstruction and airway hyperresponsiveness (AHR). Obesity is a state of chronic inflammation and is associated with metabolic complications such as diabetes mellitus and cardiovascular disease.² Many cross-sectional and longitudinal studies have shown a significant relationship between obesity and asthma.^{3,4} A recent meta-analysis of prospective studies showed a dose-dependent relationship between body mass index (BMI) and asthma.⁵ In that study, a BMI of 25–29.9 increased the odds of asthma by 38%, and obesity or a BMI of ≥ 30 increased the odds by 92% compared with normal body weight (BMI of < 25). Asthma symptom

and lung function also improved after medical or surgical weight loss.^{6,7} These study results provide additional support for the relationship between obesity and asthma. However, the relationship between obesity and AHR was conflicting in several epidemiological studies.^{8–10} Furthermore, whether adipose tissue distribution could affect the development of AHR still is not known. The aim of this study was to evaluate the effect of central obesity and abdominal adipose tissue distribution on the prevalence of AHR.

METHODS

Study Population

This study was conducted on subjects who visited the Seoul National University Hospital Gangnam Center for a routine health checkup from October 2003 to January 2009. The study protocol was approved by the Institutional Review Board of Seoul National University Hospital. To clarify the association between abdominal fat distribution and AHR, medical records of 3205 subjects who had both a methacholine bronchial provocation test (MBPT) and an abdominal CT scan were reviewed retrospectively. Of 3205 subjects, 161 subjects (5%) showed a positive result to MBPT. To select their controls, 161 subjects who corresponded with 161 subjects with AHR in terms of age and sex were randomly selected from 3044 subjects without AHR. The subjects who had current respiratory symp-

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Supported by grant 04-2005-0240 from the Seoul National University Hospital (SNUH) Research Fund

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toms, medications affecting AHR, an upper respiratory infection within the previous 6 weeks or significant comorbidities such as malignancy, heart disease, or autoimmune disease were excluded. Before the examinations, all subjects completed a questionnaire about their previous and current medical history, current medication, respiratory symptoms, and smoking status. Exsmoker was defined as those who quit smoking >1 year before enrollment in the study. Anthropometric measurements such as weight, height, and waist circumference were measured by trained personnel in our center.

Anthropometric Measurement

Weight and height were measured with the subject in light clothes without shoes. BMI was calculated as weight per the square of height (kg/m^2). Waist circumference was measured at the midpoint between the lower rib cage and iliac crest, as recommended by the World Health Organization (WHO).

Methacholine Bronchial Provocation Test

MBPT was performed using the modified Chai's method as previously described.¹¹ Briefly, forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) were measured using a spirometer (Sensor Medics 2130; Sensor Medics, San Anselmo, CA), taking the largest values of triplicate FVC and FEV_1 measurements. Subjects with respiratory tract infection during the previous 6 weeks were excluded to avoid false positive results. A Rosenthal-French dosimeter (Laboratory for Applied Immunology, Baltimore, MD) was used to deliver aerosol generated by a nebulizer (DeVilbiss, Carlsbad, CA). Subjects inhaled five breaths of increasing methacholine concentration until the FEV_1 fell to <80% of its baseline value or the highest concentration of methacholine was reached. The triplicate FEV_1 measurements were made starting at 90 seconds after each inhalation and the largest value was used for analysis. If the concentration of methacholine that caused 20% fall in FEV_1 was <25 mg/mL, the subject was considered to have AHR to methacholine.

Measurement of Abdominal Adipose Tissue Areas by CT Scan

Abdominal adipose tissue area was measured using abdominal CT scan as previously described.¹² The technique used for adipose tissue area measurement in CT cross-sectional image has been previously standardized and validated^{13–15} and has only negligible interobserver variation.^{16,17} The subjects were examined with a 16-detector row CT scanner (Somatom Sensation 16; Siemens Medical Solutions, Forchheim, Germany) in a supine position. A single slice at the level of the umbilicus measuring 5 mm in thickness

was obtained at 120 kVp and 260 mA with a scan time of 0.5 seconds. The cross-sectional surface area (in cm^2) of different abdominal fat compartment was calculated at this slice using commercially available CT software (Rapidia 2.8; INFINTT Co., Ltd., Seoul, Korea), which determined the adipose tissue area electronically by setting the attenuation values for a region of interest within a range of -250 and -50 Hounsfield units. The visceral adipose tissue area was defined as intraabdominal fat bound by the parietal peritoneum or transversalis fascia, excluding the vertebral column and paraspinal muscles. The subcutaneous adipose tissue area was defined as fat superficial to the abdominal and back muscles. Using a manual tracing method with a cursor, the visceral adipose tissue area was measured around the inner boundary of the abdominal wall muscles; the boundaries for nonadipose tissues within the visceral region, *i.e.*, bone, muscle, organs, blood vessels, and bowels were traced out, and these regions were excluded from the calculation of the visceral adipose tissue area. A region of interest drawn around the external margin of the dermis was used to calculate the area of the total adipose tissue. Subcutaneous adipose tissue area was obtained by subtracting visceral adipose tissue area from total adipose tissue area.

Statistical Analysis

Data were analyzed using the Statistical Application System statistical package, Version 9.12 (SAS Institute Inc., Cary, NC), and Marginal Homogeneity Program, Version 1.2 (Cytel Software Corp, Cambridge, MA). The paired *t*-test was used to determine the difference in BMI and waist circumference between subjects with AHR and their controls. The marginal homogeneity test was used to determine the difference in the smoking status between the two groups. The odds ratio (OR) and corresponding 95% confidence interval (CI) of each variable were calculated with conditional multiple logistic regression analysis to determine the factors associated with AHR. Statistical significance was defined as $p < 0.05$.

RESULTS

The mean age of subjects with and without AHR was 56.8 ± 10.8 (mean $\pm$ SD) years. Each group consisted of 117 men (72.7%) and 44 women (27.3%). FEV_1 , FVC, and the FEV_1/FVC ratio were significantly lower in subjects with AHR compared with their controls (Table 1). The BMI was significantly higher in subjects with AHR compared with their controls (mean $\pm$ SD, 24.56 ± 3.05 in subjects with AHR versus 23.72 ± 2.37 in their controls; $p < 0.001$). The waist circumference was also significantly higher in subjects with AHR compared with their controls (mean $\pm$ SD, 88.80 ± 9.15 in subjects

Table 1 Comparison of lung function, anthropometric measurements, and abdominal adipose tissue distribution between subjects with airway hyperresponsiveness and their controls

Variable	MBPT (+)		MBPT (–)		<i>p</i> Value*
	Mean	SD	Mean	SD	
Age (yr)	56.8	10.8	56.8	10.8	
Gender (M/F)	117/44		117/44		
FVC (%)	91.85	13.22	97.51	11.53	<0.0001
FEV ₁ (%)	91.69	11.32	104.85	13.13	<0.0001
FEV ₁ /FVC (%)	72.72	6.96	78.42	6.62	<0.0001
BMI (kg/m ²)	24.56	3.05	23.72	2.37	0.001
Waist circumference (cm)	88.80	9.15	86.49	6.98	0.001
Total fat area (cm ²)	28604.7	10851.4	26376.8	8178.1	0.012
Visceral fat area (cm ²)	13380.6	6342.0	12494.2	5569.6	0.108
Subcutaneous fat area (cm ²)	15224.1	6764.7	13882.7	5113.0	0.013

*Paired *t*-test.

BMI = body mass index; FEV₁ = forced expiratory volume in 1 s; FVC = forced vital capacity; MBPT = methacholine bronchial provocation test.

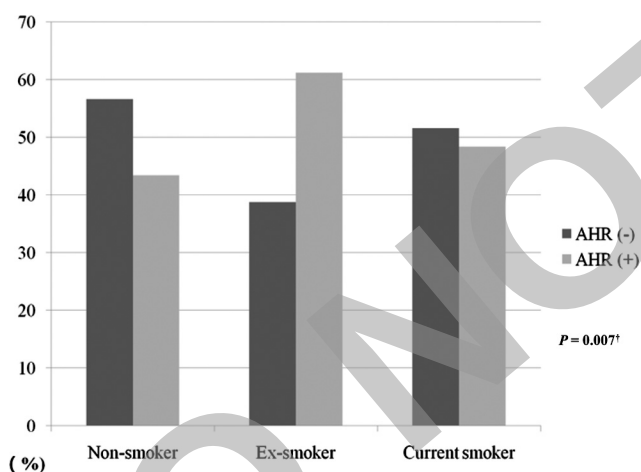


Figure 1. The relationship between smoking status and airway hyperresponsiveness.

with AHR versus 86.49 ± 6.98 in their controls; $p = 0.001$). Smoking status was significantly associated with AHR (Fig. 1). In conditional multiple logistic regression analysis, BMI was significantly associated with AHR after adjustment for smoking (Table 2; OR, 1.20; 95% CI, 1.07–1.35). Waist circumference was also significantly associated with AHR after adjustment for smoking (OR, 1.07; 95% CI, 1.02–1.11). The relationship between AHR and abdominal fat area was analyzed by means of conditional multiple logistic analysis after adjustment for smoking (Table 2). Total and subcutaneous abdominal fat were significantly associated with AHR after adjustment for smoking (OR, 1.47; 95% CI, 1.08–2.02, in the case of total abdominal fat; OR, 1.99; 95% CI, 1.19–3.31 in the case of subcutaneous fat), but visceral fat was not. The relationship between AHR and the abdominal fat area was analyzed according to gender.

Table 2 Risk of airway hyperresponsiveness associated with obesity measures and abdominal fat distribution

Variable	OR	95% CI		<i>p</i> Value*
Body mass index	1.20	1.07	1.35	0.002
Waist circumference	1.07	1.02	1.11	0.003
Total fat area	1.47	1.08	2.02	0.015
Visceral fat area	1.39	0.86	2.26	0.18
Subcutaneous fat area	1.99	1.19	3.31	0.008

*Conditional logistic regression analysis after adjustment for smoking.

BMI = body mass index; CI = confidence interval; OR = odds ratio.

BMI and waist circumference was significantly associated with AHR in both men and women (Table 3). In women, there was no association between AHR and abdominal fat distribution. However, subcutaneous fat was significantly associated with AHR in men (OR, 2.05; 95% CI, 1.04–4.03).

DISCUSSION

To our knowledge, this is the first study to show a significant association between subcutaneous abdominal fat and AHR. Our study also showed that central adiposity was significantly associated with AHR.

Obesity has been associated with AHR, which is the most characteristic feature of asthma, in a few clinical studies. A prospective cohort study of 61 adult men showed that the BMI in the lowest quintile (BMI, 19.3–24.3) and in the highest quintile (BMI, >29.4) was significantly associated with the devel-

Table 3 Risk of airway hyperresponsiveness associated with obesity measures and abdominal fat distribution according to gender

Variable	OR	95% CI	p Value*
Male			
Body mass index	1.16	1.02 1.32	0.026
Waist circumference	1.05	1.01 1.10	0.030
Total fat area	1.39	0.97 2.00	0.077
Visceral fat area	1.27	0.76 2.11	0.360
Subcutaneous fat area	2.05	1.04 4.03	0.037
Female			
BMI	1.41	1.05 1.89	0.022
Waist circumference	1.17	1.02 1.34	0.028
Total fat area	1.84	0.97 3.46	0.061
Visceral fat area	3.07	0.67 14.04	0.150
Subcutaneous fat area	2.03	0.90 4.59	0.088

*Conditional logistic regression analysis after adjustment for smoking.

BMI = body mass index; CI = confidence interval; OR = odds ratio.

opment of AHR.⁸ Furthermore, a high BMI (BMI, >29.4) increased the odds of AHR by 10 times. The study of the European Community Respiratory Health Survey of 11,277 subjects showed that AHR increased with increasing BMI, especially in men.⁹ In contrast, the study result of Schachter *et al.* was different from the former studies.¹⁰ In this study, obesity was a risk for asthma and wheezing, but not for AHR. However, information about the type or dose of medication was not available, and inhaled corticosteroids may have affected the outcome of the study if obese asthma patients received a sufficient dose of inhaled corticosteroids to reduce AHR. In our study, BMI increased the odds of AHR by 20% after adjustment for smoking. This result was consistent with the former clinical studies that showed an association between obesity and AHR and further supports the significance of obesity in the development of AHR. Most studies about obesity use BMI as a marker for obesity because it is cheap and simply measured. However, BMI has a few problems if the definition of overweight and obesity based on BMI cutoff points recommended by the WHO were applied to different populations. First, the association among BMI, percentage of body fat, and body fat distribution was very different across populations.¹⁸ Second, the cutoff points for the increased risk of type 2 diabetes and cardiovascular disease varied from 22 to 25 kg/m² across different Asian countries.¹⁹ Therefore, the difference of BMI between the group with AHR and the control group in our study may be meaningful considering the limitation of BMI

measurement to assess the degree of obesity and the ethnic difference of the observed risk of type 2 diabetes and cardiovascular disease regardless of BMI cutoff points recommended by WHO although further studies are warranted. In contrast, waist circumference and the waist-to-hip ratio are better surrogate markers for abdominal obesity more than BMI because they correlate well to abdominal fat deposition.²⁰ Our study showed that waist circumference increased the odds of AHR by 7% after adjustment for smoking, suggesting that central obesity may be an important factor in the development of AHR. In addition to anthropometric measurements, regional fat distribution can be measured by dual-energy x-ray absorptiometry, abdominal ultrasonography, abdominal CT, or MRI.²¹ The current gold standard methods of these methods are abdominal CT and MRI technique. In our study, abdominal fat distribution was objectively measured by abdominal CT scan. Total and subcutaneous abdominal fat significantly increased the risk of AHR, but visceral fat did not. This association of subcutaneous fat with AHR was consistent, especially in men. The cause for the lack of association between AHR and abdominal obesity is uncertain in our study. This may be attributed to relatively small sample size of women in our study or other confounding factors such as menopausal status that was not known in our study.²²

Chronic inflammation, mechanical factors, comorbidities related to obesity, and common genetic etiology have been suggested as the mechanism of asthma in obese subjects.²³ Adipose tissue is an endocrine organ that produces many cytokines and hormones rather than an organ merely accumulating fat mass.^{2,23} Visceral fat is a more active site of inflammation than subcutaneous fat and is associated with metabolic complications such as diabetes mellitus, hypertension, and cardiovascular disease.^{24,25} However, subcutaneous fat produces different kinds of adipokines other than those of visceral fat, which suggests that subcutaneous fat may be associated with pathological conditions other than metabolic syndrome and its complications.^{26,27} Leptin is mainly produced by human subcutaneous fat, and tumor necrosis factor (TNF) α is produced in equal amounts by human subcutaneous and visceral fat.²⁷ Serum leptin level increased in asthma patients.^{28,29} Furthermore, the administration of leptin increased allergen-induced AHR and Th2 cytokine expression in an animal model of asthma.³⁰ TNF- α level also increased in the airway of asthma patients.³¹ The administration of inhaled recombinant TNF- α to patients with mild asthma led to increased AHR, airway neutrophilia, and eosinophilia.³² A recent study reported that intercellular cell adhesion molecule 1 increased in obese asthmatic children, suggesting the role of endothelial activa-

tion on the pathogenesis of asthma in obese subjects.³³ In our study, the subcutaneous fat measured by abdominal CT scan was significantly associated with AHR. Adipokines such as leptin or TNF- α from subcutaneous abdominal fat may contribute to the development of AHR, although those cytokines were not measured in the study.

In obese subjects, functional residual capacity is reduced because of the change in elasticity of the chest wall. Tidal volume is also reduced in obese subjects. These changes may reduce strain on airway smooth muscles and increase the stiffness of them. The net result is shortening of airway smooth muscles and consequent increase in AHR.²³ This decrease in lung volumes was associated with AHR in obese men but not in women.³⁴ The increase of abdominal subcutaneous fat in obese subjects may imply the increase of subcutaneous fat in parts of the body other than the abdomen. There is a possibility that the increase of subcutaneous fat in the chest wall may decrease the compliance of the chest wall, and finally increase AHR in obese subjects, although the amount of subcutaneous fat in the chest wall was not measured in this study.

Dietary restriction is the most widely used weight reduction strategy. Weight reduction may prevent the development of asthma in obese subjects through reduction of subcutaneous fat because subcutaneous fat was significantly associated with AHR. Weight reduction may be more beneficial for women than men because women lose more subcutaneous abdominal fat for a given reduction in body weight or waist circumference than men.³⁵ Weight reduction may also be helpful to obese asthmatic patients through reduction of AHR.

There were several limitations of this study. First, the mechanism about the relationship between subcutaneous abdominal fat and AHR was not revealed because the adipokines related to asthma or the amount of subcutaneous fat in the chest wall was not measured in the study. Second, this study had a cross-sectional design. For this reason, the effect of subcutaneous fat on the later development of asthma could not be evaluated although subcutaneous fat was significantly associated with AHR.

To reveal the mechanism about the relationship between subcutaneous fat and AHR, a future study that measures adipokines related to asthma is needed. A study on weight reduction in obese people with AHR is also required to show the protective effect of weight reduction on AHR and the later development of asthma.

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