

Sensitization to House Dust Mites: Association with Airway Hyperresponsiveness in Mite-Sensitive Young Adults with Asthma

Woo-Jung Song^{1,2}, Chin Kook Rhee³, Se-Min Hwang⁴, Ji Eun Lee⁵, Sang Heon Cho^{1,2} and Sang Min Lee⁶

¹Department of Internal Medicine, Seoul National University College of Medicine, ²Institute of Allergy and Clinical Immunology, Seoul National University Medical Research Center, ³Department of Internal Medicine, The Catholic University of Korea College of Medicine, ⁴Department of Health Promotion, Gangbuk-gu Community Health Center, Seoul, ⁵Department of Internal Medicine, Armed Forces Capital Hospital, Seongnam, ⁶Department of Medicine, Gachon University Gil Medical Center, Incheon, Korea

Background: The aim of this study was to evaluate the correlation between sensitization to mite and airway hyperresponsiveness in mite-sensitive young adults with asthma. **Methods:** This study included 72 young male Korean conscripts aged between 19 and 30 years who complained of recurrent wheezing and dyspnea with nocturnal aggravation and no history of other lung disease, asthma exacerbation, or treatment against asthma except short-acting beta2 agonists over the last 2 months. They underwent pulmonary function tests and methacholine challenge tests. In 63 subjects, the forced expiratory volume in 1 second was more than 60% of the predicted value, and the provocative concentration of methacholine causing a 20% decline in forced expiratory volume in 1 second in methacholine challenge tests was less than 16 mg/mL. Serum was collected from these subjects to measure specific immunoglobulin E against *Dermatophagoides farinae* and *Dermatophagoides*

pteronysinus using the AdvanSure Allergy Screen test.

Results: Specific immunoglobulin E against *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* correlated negatively with provocative concentration of methacholine causing a 20% decline in forced expiratory volume in 1 second in 50 subjects who were mite-sensitive ($\gamma = -0.368$, $P=0.009$; and $\gamma = -0.415$, $P=0.003$, respectively). However, specific immunoglobulin E against *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* was not correlated with forced vital capacity, forced expiratory volume in 1 second, or forced expiratory volume in 1 second/forced vital capacity.

Conclusion: Sensitization to mites may correlated with airway hyperresponsiveness in mite-sensitive young adults with asthma. (Korean J Asthma Allergy Clin Immunol 2012; 32:183-189)

Key words: Asthma; *Dermatophagoides farinae*; *Dermatophagoides pteronyssinus*; Sensitization

INTRODUCTION

Sensitization to house-dust mites (HDM) including *Dermatophagoides farinae* (Df) and *D. pteronyssinus* (Dp) is a significant and independent risk factor for the development of asthma in areas where HDM proliferate.^{1,2} Moreover, exposure to mite allergens is related to the severity of asthma.^{3,4}

Asthma is a chronic inflammatory airway disease characterized by airway hyperresponsiveness (AHR) and reversible airflow obstruction.⁵

With regard to the relationship between asthma and sensitization to mites, AHR is sensitive to changes in exposure to relevant allergens.⁶⁻⁹ Thus, in individuals with a genetic predisposition who live in an area with sufficient HDM proliferation, exposure to mite allergens can result in sensitization, followed by the development of AHR and subsequent asthma.¹⁰ However, previous studies have reported that the degree of AHR was not correlated with the degree of sensitization to mite allergens.¹¹⁻¹³ In a community-based study, allergy to HDM was associated with reduced lung-function parameters including forced expiratory volume in 1 second (FEV₁) and the ratio of FEV₁ to vital capacity.^{14,15} However, the relationship between sensitization to mite allergen and reduced lung function has been controversial in studies of asthmatic patients.¹⁶⁻¹⁸

The prevalence of wheezing, a classic symptom of asthma, among young conscripts in the Korean military has been reported to be 10.5%, and the prevalence of current asthma in one area of the

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Correspondence : Sang Min Lee, Department of Medicine, Gachon University Gil Medical Center, 21, Namdong-daero 774beon-gil, Namdong-gu, Incheon 405-760, Korea
Tel: +82-32-460-8930, Fax: +82-32-469-4320
E-mail: allergylung@gilhospital.com

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military was estimated to be 9.1%.¹⁹⁾ The authors suggested that a family history of allergic disease, overweight, current smoking, current allergic rhinoconjunctivitis, and current eczema were risk factors for wheezing. However, the study did not evaluate whether sensitization to aeroallergens including HDM could be a risk factor for asthma symptoms because a skin-prick test and measurement of serum specific immunoglobulin E (IgE) against aeroallergens were not performed.

The present study aimed to evaluate the relationship between sensitization to the HDM allergen and AHR in mite-sensitive young adults with asthma in the Korean military.

MATERIALS AND METHODS

1. Subjects

We recruited young male Korean military conscripts aged from 19 years to 30 years who visited Armed Forces Capital Hospital complaining of recurrent wheezing and dyspnea with nocturnal aggravation who had no history of other airway or lung disease, asthma exacerbation and who had not received treatment against asthma within last 2 months, with the exception of short-acting beta2 agonist (SABA). All participants provided informed consent. Participants were requested to complete a questionnaire regarding smoking status and the existence of combined allergic rhinitis, which have been associated with AHR.²⁰⁾

2. Study design

After recruitment, the participants underwent a basal pulmonary function test (PFT) and a subsequent methacholine challenge test (MCT). The parameters of the basal PFT included forced vital capacity (FVC), FEV₁, and FEV₁/FVC. Subjects with severe airway obstruction whose FEV₁ was less than 60% of the predicted value were excluded before the MCT. AHR was defined as a provocative concentration of methacholine causing a 20% decline in FEV₁ (PC₂₀) in the MCT < 16 mg/mL, and subjects with AHR were included as asthma patients.^{21,22)} Serum was collected to measure the level of specific IgE against inhalant allergens including *Df* and *Dp*. Subjects in whom specific IgE against *Df* or *Dp* was class I or higher (>0.35 IU/mL) were enrolled in the study to evaluate the relationship between sensitization to HDM and AHR.

3. Pulmonary function test

PFT was performed using a Sensor Medics 2130 (SensorMedics Corporation, Yorba Linda, CA, USA). FVC and FEV₁ were recorded

according to American Thoracic Society (ATS) recommendations. The higher of two values for FEV₁ (reproducible within 100 mL) was recorded and percentages of predicted FEV₁ values were calculated.

4. Methacholine challenge test

The MCT was conducted using dosimeter method, as the ATS guidelines recommended.²¹⁾ Briefly, methacholine was inhaled during inspiration using an automatic nebulizing device (NE-U17; Omron, Kyoto, Japan) and dosimeter (NSPIRE; Longmont, CO, USA) until a PC₂₀ was obtained or a concentration of 16 mg/mL was reached. Subjects were requested not to use SABA on the day of MCT.

5. Measurement of specific IgE against inhalant allergen

Serum-specific IgE against *Df* and *Dp* was measured using the AdvanSure Allergy Screen (LG Life Science, Seoul, Korea).^{23,24)} The degree of sensitization against *Df* and *Dp* were graded from class 0 to class VI according to the titer of serum-specific IgE against *Df* and *Dp* (class 0: 0.00~0.34 IU/mL, class 1: 0.35~0.69 IU/mL, class 2: 0.70~3.49 IU/mL, class 3: 3.50~17.49 IU/mL, class 4: 17.50~49.99 IU/mL, class 5: 50.00~99.99 IU/mL, class 6: ≥100 IU/mL).

6. Statistical analysis

The correlations between specific IgE against *Df* and *Dp* and the other continuous variables were evaluated using Spearman's rank correlation coefficient. PC₂₀ was compared according to smoking status and the existence of combined allergic rhinitis using Kruskal-Wallis test and Mann-Whitney *U*-test, respectively. The statistical analyses were performed using the Statistical Package for the Social Sciences software (SPSS ver. 12.0, SPSS Inc., Chicago, IL, USA). A *P* value < 0.05 was deemed to indicate statistical significance.

7. Ethics statement

The research protocol was approved by the ethics committee of the Armed Forces Medical Command (ROK-MND-2009-KMMRP-015).

RESULTS

1. Demographic and clinical characteristics of subjects

A total of 72 subjects complaining of recurrent wheezing and

dyspnea with nocturnal aggravation who had no history of other airway or lung disease, asthma exacerbation or asthma treatment other than SABA within the last 2 months underwent basal PFT (Fig. 1). In two subjects, FEV₁ was below 60% of the predicted value, and they were excluded from the study. The remaining 70 subjects underwent a subsequent MCT. Of those, 63 had a positive MCT, with a PC₂₀ less than 16 mg/mL. Serum was collected in

these subjects to measure serum-specific IgE antibodies against inhalant allergens. The presence of specific IgE against *Df* or *Dp* indicated a class I or higher allergy in 50 subjects (Table 1). Among them, there was none in whom specific IgE against *Df* or *Dp* indicated a class 0. Demographic characteristics and the results of the basal PFT and MCT are shown in Table 2.

2. Correlation between specific IgE against mite allergens and AHR or lung function

Specific IgE against *Df* and *Dp* was negatively correlated with PC₂₀ (Fig. 2). However, it was not correlated with FVC, FEV₁, or FEV₁/FVC (Table 3). PC₂₀ was not correlated with age or symptom duration ($\gamma = -0.116$, $P=0.424$; $\gamma = -0.057$, $P=0.709$, respectively). Furthermore, PC₂₀ was not significantly different between subjects with and without combined allergic rhinitis ($P=0.193$) or among current smokers, former smokers, and never smokers ($P=0.917$).

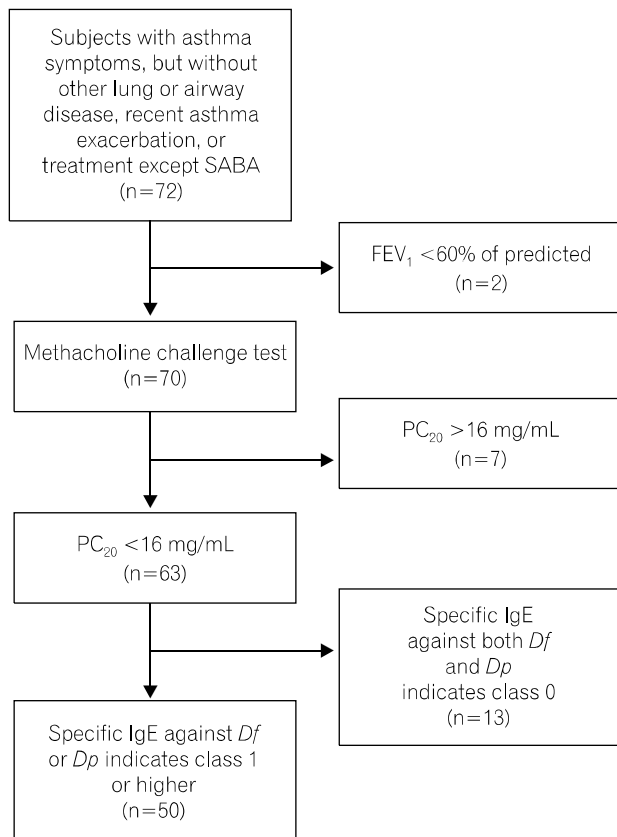


Fig. 1. Flowchart of the enrollment process. SABA = short-acting beta2 agonist; FEV₁ = forced expiratory volume in 1 second; PC₂₀ = a provocative concentration of methacholine causing a 20% decline in FEV₁; IgE = immunoglobulin E; *Df* = *Dermatophagoides farinae*; *Dp* = *Dermatophagoides pteronyssinus*.

Table 2. Demographic characteristics

Variable	Value
Age (yr)	21 (19~30)
Male	50 (100)
Symptom duration (mo)	54 (1~240)
Combined allergic rhinitis	41 (82)
Smoking status	
Current smoker	25 (50)
Former smoker	7 (14)
Never smoker	18 (36)
Basal pulmonary function test	
FVC (%predicted)	96.6 (58.7~152.0)
FEV ₁ (%predicted)	92.7 (65.6~136.5)
FEV ₁ /FVC	80.2 (54.4~99.2)
PC ₂₀ in methacholine challenge test	2.46 (0.087~14.7)

Values are presented as median (range) or n (%). FVC = forced vital capacity; FEV₁ = forced expiratory volume in 1 second; PC₂₀ = a provocative concentration of methacholine causing a 20% decline in FEV₁.

Table 1. Results of the Advansure Allergy Screen (LG Life Science, Seoul, Korea) test to mite allergens according to class

Allergen	Serum specific IgE					
	Class I	Class II	Class III	Class IV	Class V	Class VI
<i>Df</i>	13 (26)	4 (8)	4 (8)	23 (46)	4 (8)	2 (4)
<i>Dp</i>	16 (32)	4 (8)	5 (10)	22 (44)	1 (2)	2 (4)

Values are presented as number (%). IgE = immunoglobulin E; *Df* = *Dermatophagoides farinae*; *Dp* = *Dermatophagoides pteronyssinus*.

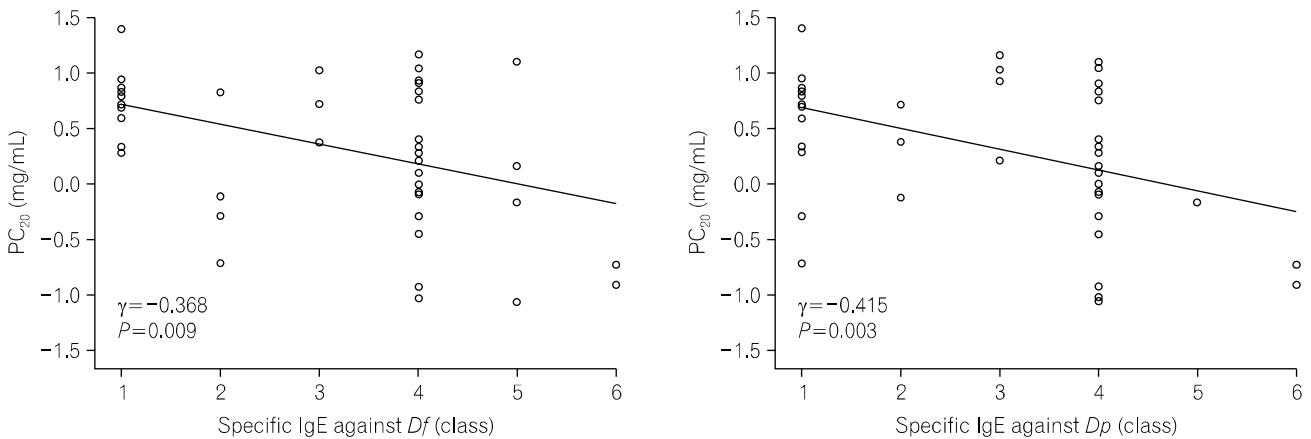


Fig. 2. Correlation between PC₂₀ in the methacholine challenge test and specific IgE class against mite allergens. PC₂₀ was logarithmically transformed. PC₂₀ = a provocative concentration of methacholine causing a 20% decline in forced expiratory volume in 1 second; IgE = immunoglobulin E; *Df* = *Dermatophagoides farinae*; *Dp* = *Dermatophagoides pteronyssinus*.

Table 3. Correlation between specific immunoglobulin E class against mite allergens and parameters of the basal pulmonary-function test

Parameters	Serum specific IgE			
	Specific IgE against <i>Df</i> (class)		Specific IgE against <i>Dp</i> (class)	
	γ	<i>P</i> value	γ	<i>P</i> value
FVC (%predicted)	0.232	0.104	0.251	0.079
FEV ₁ (%predicted)	0.156	0.280	0.191	0.184
FEV ₁ /FVC	0.010	0.945	0.030	0.839

IgE = immunoglobulin E; *Df* = *Dermatophagoides farinae*; *Dp* = *Dermatophagoides pteronyssinus*; FVC = forced vital capacity; FEV₁ = forced expiratory volume in 1 second.

DISCUSSION

AHR is a characteristic feature of asthma.¹⁰⁾ Changes in natural allergen exposure and changes during allergen-inhalation provocation challenges are often followed by changes in the degree of AHR, particularly in young asthmatic patients.^{6-8,25)} Community-based studies have shown that AHR is clearly associated with allergen sensitization, particularly to HDM.¹⁰⁾ A study conducted in German school children reported an increased risk of bronchial response to exercise in children sensitized to HDM, whereas sensitization to animal dander was not a risk factor.²⁶⁾ A similar result was found in a random population of 527 Danish children and adolescents.²⁷⁾ In children from New Zealand, sensitization to cat and dog dander and to HDM was found to be an independent risk factor for AHR as measured by the MCT.²⁸⁾

Two Japanese studies failed to find a significant correlation between the degree of AHR and the degree of sensitization to mite allergens.^{11,12)} However, those studies could not completely rule out an effect of asthma medication including corticosteroid, which can influence the relationship between AHR and sensitization to mite allergens in asthmatic patients.¹⁰⁾ Moreover, one of the Japanese studies did not assess smoking status, which could be a confounding factor affecting AHR,¹¹⁾ and the other study included *Df*-sensitive non-asthmatic subjects.¹²⁾ A recent Chinese study reported that the PC₂₀ in the MCT was not significantly correlated with specific IgE to D1 and D2.¹³⁾ However, the subjects' symptoms were not typical of asthma. They complained of persistent cough and/or unexplained episodes of dyspnea, but they did not report wheezing or nocturnal aggravation, which are hallmark symptoms of asthma. Moreover, the PC₂₀ cut-off value of was not strict (25 mg/mL), so subjects without asthma may have been enrolled in the study. In addition, the Chinese study did not identify current medication, combined allergic rhinitis, or smoking status, all of which may influence the relationship between sensitization to mites and AHR in asthmatic patients.^{10,20)} Consequently, the Japanese and Chinese studies did not control for the effects of possible confounding factors and did not provide sufficient evidence of a relationship between atopic sensitization to mites and AHR in asthma patients.

Our study enrolled young adults complaining of recurrent wheezing and dyspnea with the nocturnal aggravation typical of asthma. The PC₂₀ cut-off value in our study was relatively strict (16 mg/mL), reducing the likelihood of a false positivity for asthma.^{21,22)} Furthermore, we excluded subjects who had used asthma medication, with the exception SABA within the last 2

months, to control for the influence of medication. We demonstrated that smoking status and combined allergic rhinitis were not confounding factors in our study by showing that the existence of combined allergic rhinitis and smoking status did not significantly affect AHR.

The relationship between sensitization to mites and lung function (FEV_1 , peak expiratory flow [PEF]) is less clear and may have been obscured by pharmacotherapy with inhaled steroids and the resulting improvement in lung function.¹⁰⁾ The Second National Health and Nutrition Survey in the United States (NHANES II) reported a significant association between skin-test reactivity to HDM and decrements in FEV_1 in a random sample of children with asthma or frequent wheezing.¹⁷⁾ In a British study, Clough et al¹⁸⁾ reported a similar result investigating skin sensitivity to a panel of common allergens rather than skin sensitivity to HDM alone. Furthermore, Clough et al¹⁸⁾ found that variation in PEF was associated with the degree of skin sensitivity to common allergens. However, no relationship was found between the predicted FEV_1 % and skin test reactivity to mites or to other allergens in the Tucson (Arizona) Study of 261 patients with diagnosed asthma.¹⁶⁾

We found no significant correlation between lung function and specific IgE class against mite allergens. However, the primary end-point of our study was the correlation between sensitization to mites and AHR, not lung function in asthma. We excluded two subjects with severe airway obstruction whose FEV_1 was less than 60% of the predicted value before MCT. As a result, most of the subjects in our study presented normal or near-normal lung function. Our study included seven subjects whose FEV_1 was less than 80% of the predicted value, and the lowest FEV_1 in our study was 66% of the predicted value. Furthermore, it is likely that young asthma patients who had severe airway obstruction or disease activity were exempted during conscription and would not have been enrolled in our study. According to Korean military regulations, patients with severe persistent asthma who were hospitalized for acute asthma exacerbation more than twice within a last year should be exempted during conscription. Consequently, we cannot conclude that sensitization to mites is not associated with lung function in people with asthma because our sample did not include asthma patients with severe airway obstruction or severe disease activity.

The present study has some other limitations. The age range of the male Korean military conscripts enrolled in our study was 19~30 years old; thus, the study population was not representative of people outside that age group or of females. We could not

comprehensively evaluate the correlation between sensitization to other inhalant allergens and AHR or lung function in asthma. Of the 63 subjects with a positive MCT, Df and Dp were the most prevalent allergens associated with class I or higher allergies. The AdvanSure Allergy Screen test revealed 50 subjects in this category. The second most prevalent allergen was mugwort, and the AdvanSure Allergy Screen test revealed class I or higher mugwort allergies in only five subjects. AHR and lung function were not correlated with sensitization to any inhalant allergen other than Df and Dp in subjects with a positive MCT. It may be that other allergens have less effect on AHR than HDM does; however, we would have had to enroll several more subjects in our study had we intended to evaluate the correlation between sensitization to inhalant allergens other than HDM and AHR or lung function in asthma.

Despite those limitations, our study has some merits. The subjects in our study were young adults with a mean age of 21 years. At this age, we could exclude the possibility of other diseases such as chronic obstructive pulmonary disease, which occur in older age groups, and childhood viral infections of the lower respiratory tract, which are frequently confused as asthma. Those conditions are confounding factors that could weaken the correlation between sensitization to mites and AHR in people with asthma. Moreover, the aging process and disease progression are likely to have been relatively short in our young subjects, so irreversible airflow obstruction, which may be a confounding factor, was less likely. Furthermore, we recruited only subjects who had no history of asthma treatment within the last 2 months, with the exception of SABA. Thus, we could exclude the possible influence of medication on the relationship between sensitization to mites and AHR or lung function.¹⁰⁾ Finally, we were able to rule out smoking status and combined allergic rhinitis as confounding factors in our study, as AHR was not significantly affected by smoking status or the existence of combined allergic rhinitis.

CONCLUSION

Sensitization to mites is correlated with AHR in mite-sensitive young adults with asthma.

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