

Correlation Between Inhalant Allergen-Specific IgE and Pulmonary Function in Children With Asthma

Sung-Yon Choi, MD,¹ Myung Hyun Sohn, MD, PhD,¹ Hye-Yung Yum, MD, PhD,²
Byoung-Chul Kwon, MD,¹ and Kyu-Earn Kim, MD, PhD^{1*}

Summary. Sensitization to aeroallergens is associated with diminished lung function in adults. Little has been studied on the relationship between the inhalant allergen-specific IgE and pulmonary function in asthmatic children. This study was focused on four major inhalant allergens found in Korea, including *Dermatophagoides pteronyssinus* (*Der p.*), *Dermatophagoides farinae* (*Der f.*), and *Alternaria*- and German cockroach-specific IgEs, with evaluation of pulmonary function in relation to the amount of allergens. The parents or legal guardians of participants enrolled in this study gave informed consent. Fifty-five asthmatic patients and 48 nonasthmatic children were included. The amounts of specific IgE for the four specified inhalant allergens were determined by employing the CAP system FEIA. Forced expiratory volume in 1 sec (FEV₁)/forced vital capacity (FVC), FEV₁, and forced expiratory flow between 25% and 75% of FVC (FEF_{25–75}) of subjects were evaluated through pulmonary function tests. In the asthmatic group, FEV₁, FEV₁/FVC, and FEF_{25–75} were significantly reduced ($P < 0.05$): reduction in FEV₁ ($r = -0.44$) and FEF_{25–75} ($r = -0.33$) in association with the *Der f.*-specific allergen, and reduction in FEV₁ ($r = -0.37$) and FEF_{25–75} ($r = -0.34$) in association with the *Der p.*-specific allergen, were observed. However, there was no significant correlation with German cockroach and *Alternaria* allergen. In the control group, no significant correlation was detectable between the allergen-specific IgE titers and the results of pulmonary function tests. In asthmatic patients, *Der p.*- and *Der f.*-specific IgEs, and not German cockroach and *Alternaria*, seem to play a considerable role in reduced pulmonary function among asthmatic children. **Pediatr Pulmonol.** 2005; 39:150–155. © 2005 Wiley-Liss, Inc.

Key words: house dust mite; asthma; inhalant allergen; pulmonary function test; specific IgE.

INTRODUCTION

House dust mite, cockroach, pets (e.g., cats and dogs), and mold are indicated as representative allergens,^{1,2} and sensitization to these inhalant allergens was associated with reduced pulmonary function in adult asthmatic patients.^{3–5} Indeed, 90% of children with asthma were reported to be sensitized to these inhalant allergens.⁶ Gergen and Turkeltaub⁷ reported on the association of exposure to inhalant allergens, such as house dust and *Alternaria*, with adult asthma, and several reports suggested that sensitization to *Alternaria* allergen is closely related to schoolchildren with asthma.^{8–11} An increase of serum IgE against *Aspergillus fumigatus* in children can be a risk factor for decreased FEV₁ and FEF_{25–75},¹² and the exposure to house dust, dog fur, and oak trees in children between ages 6–12 years reduced FEV₁.^{13,14} Meanwhile, Nelson et al.¹⁵ suggested that exposure to house dust mite or cockroach allergen is not correlated with hypersensitivity to metacholine, but is linked with cat fur, dog fur, or *Alternaria*. As described above, correlations between degrees of exposure to inhalant allergens and reduction of pulmonary function were variously reported.

As for the mechanism of inhalant allergens inducing asthma, the underlying mechanism of asthma is airway

inflammation, and chronic inflammation might lead to airway remodeling.^{16,17} Studies in animals demonstrated structural remodeling changes occurring in the airways of rats that were sensitized and chronically exposed to allergens.¹⁸ Exposure to high levels of allergens in sensitized asthmatic patients caused a worsening of pulmonary function in experimental studies.¹⁷ However, the correlation between allergen-specific IgE values and reduction of pulmonary function in children has not been definitely clarified.

¹Department of Pediatrics and Allergy Institute, Yonsei University College of Medicine, Seoul, Korea.

²Department of Pediatrics, College of Medicine, Pochon Cha University, Seoul, Korea.

S-Y Choi and MH Sohn contributed equally to this work.

*Correspondence to: Kyu-Earn Kim, M.D., Ph.D., Department of Pediatrics, Yonsei University College of Medicine, Youngdong Severance Hospital, P.O. Box 1217, Seoul 135-270, Korea. E-mail: kekim@yumc.yonsei.ac.kr

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Therefore, in the current study, we grouped subject children into asthmatic and nonasthmatic control groups, and then investigated the possible correlation between the degree of sensitization to allergens and asthma by measuring each IgE value against such specific inhalant allergens as *Dermatophagoides pteronyssinus* (*Der p.*), *Dermatophagoides farinae* (*Der f.*), *Alternaria*, and cockroach. Next, three pulmonary function indices, FEV₁, FEV₁/FVC, and FEF_{25–75}, known to well indicate airway obstruction in both asthmatic and nonasthmatic children, were measured and compared. Finally, the levels of pulmonary function reduction vs. specific IgE values against each allergen were observed and examined, and the correlation between these two parameters was evaluated.

MATERIALS AND METHODS

Study Subjects

This study was performed with patients who visited the allergy clinic for evaluation of nonspecific upper respiratory symptoms or a general health workup or typical symptoms of asthma at the Severance Hospital of Yonsei University from October 2001–December 2002. The diagnosis of asthma was made on the basis of American Thoracic Society (ATS) criteria.¹⁹ The children with asthma reported having typical wheezing or episodic shortness of breath, and showed reversible airflow limitation or airway hyperresponsiveness to methacholine in the absence of airflow limitation. The control subjects were age-matched healthy children who had neither asthmatic symptoms nor a hypersensitivity reaction to methacholine. The questions concerned the presence of the following asthma-related symptoms: chest tightness, difficulty breathing, occasional or persistent wheeze, breathlessness or cough after exposure to cold air or exercise, chest noise while breathing, chronic cough persisting for more than 3 weeks, and nocturnal symptoms that disturb sleep.²⁰ If any questions were answered positively or could not be answered confidently, the children were excluded from the control subjects. Fifty-five asthmatic patients constituted the asthmatic group, and the normal group included 48 children. They were over 7 years old and capable of undergoing pulmonary function tests. At the initiation of the study, a physical examination, blood sampling, and pulmonary function tests were performed on all subjects.

Specific IgE Test

A specific IgE test was performed on house dust mites (*Der p.* and *Der f.*), *Alternaria*, and German cockroach, four common allergens in Korea, by using the CAP system FEIA (Pharmacia, Diagnostics, Uppsala, Sweden). A specific IgE value over 0.35 KU_A/l was considered positive.

Pulmonary Function Test

Spirometric measurements were performed according to ATS criteria.²¹ Temperature and atmospheric pressure were measured during the pulmonary function test, and a leak test was taken before the pulmonary function test. Quality control was performed with a 3-l syringe calibration. Spirometry was performed after withholding antihistamine for 3 days and inhaled bronchodilators for 6 hr. A pulmonary function test was conducted on subjects in standing postures who were clinically stable without any manifestations of dyspnea and wheezing on physical examination at time of testing. FEV₁, FEV₁/FVC, and FVC were measured with a Microlab 3300 Spirometer (Micro Medical Ltd., UK) connected by computer and calibrated according to age, sex, height, weight, and race,²² and are expressed in percent predicted.

Statistical Analysis

All analyzed data are represented as mean $\pm$ standard deviation (SD). First, estimated values of pulmonary function tests were arranged into the asthmatic group and the control group for the comparison of differences between groups by unpaired Student's *t*-test. The positive figures against each inhalant allergen in the two groups were compared through Pearson chi-square test and then analyzed to evaluate the relationship between inhalant allergens and asthma. Next, the values of three pulmonary function tests were evaluated according to each allergen-specific IgE value, and were compared to verify differences in the relationship between the amount of allergens and the reduction of pulmonary function. Finally, correlation coefficients were obtained through Pearson correlation. Every value had statistical significance within only $P < 0.05$.

RESULTS

Characteristics of Subjects

Study subjects included 55 children in the asthmatic group and 48 children in the control group, who came to the allergy clinic at Severance Hospital from October 2001–December 2002. Forty boys and 15 girls were in the asthmatic group, and 35 boys and 13 girls were in the

TABLE 1—Characteristics of Subjects¹

	Asthmatic group	Control group
Number of subjects	55	48
Average age (years)	10.5 $\pm$ 1.9 (6.9–15.3)	10.9 $\pm$ 3.4 (6.8–17)
Gender (male:female)	40:15	35:13
Total IgE (KU _A /l) ²	232.1 (2.8–4,656)	122.9 (2–1,556)

¹Data are expressed as mean $\pm$ standard deviation or number of subjects.

²Mean IgE values are geometric means. Parentheses express range of values.

TABLE 2—Differences of Pulmonary Function Between Asthmatic Group and Control Group¹

Variable	Asthmatic group	Control group
Corrected FEV ₁ (%)	75.8 ± 15.3*	86.4 ± 13.8
FEV ₁ /FVC (%)	87.6 ± 8.1*	95.0 ± 5.1
Corrected FEF _{25–75%} (%)	77.4 ± 25.6*	102.7 ± 23.2

¹Data are expressed as mean ± standard deviation. Parameters of pulmonary function tests were adjusted for age, sex, height, weight, and race, and are expressed in percent predicted. *P*-values were calculated by unpaired Student's *t* test.

**P* < 0.05 vs. controls.

control group. The average age was 10.5 years in the asthmatic group, and 10.9 years in the control group (Table 1).

Comparison of Pulmonary Function Between Asthmatic and Control Groups

As listed in Table 2, all mean FEV₁, FEF_{25–75}, and FEV₁/FVC values were found to be significantly decreased in the asthmatic group compared to the control group.

Comparison of Allergen-Specific IgE Positive Rates Between Asthmatic and Control Groups

When examined for a positive reaction of specific IgEs to four inhalant allergens, the asthmatic group showed higher specific IgE values for *Der p.*, *Der f.*, and German cockroach than did the control group (Table 3).

Correlation Between Allergen-Specific IgE Values and Pulmonary Function

In the asthmatic group, the values of FEV₁, FEF_{25–75}, and FEV₁/FVC showed reduced pulmonary function with the increase of allergen-specific IgE. As shown in Figures 1 and 2, the results for the *Der f.* allergen revealed that the values of FEV₁ and FEF_{25–75} were significantly decreased as the allergen-specific IgE level increased, and similar decreases were also found for the *Der p.* allergen (*P* < 0.05). On the other hand, there was no significant difference in German cockroach and *Alternaria* allergen (Table 4). In the control group, there was no significant

association of each allergen-specific IgE with pulmonary function (data not shown).

DISCUSSION

When an atopic allergic person is sensitized to any inhalant allergen, the inhalant allergen induces an allergic inflammatory reaction on airway mucosa.^{5,8,16} Airway inflammation may be variably associated with changes in airway hyperresponsiveness, airflow limitation, respiratory symptoms, and disease chronicity.²³ In Korea, all adults and children with allergy are highly sensitized to *Der p.* and *Der f.* (house dust mites), and the sensitized antigens can be causal allergens of asthma. Platts-Mills et al.²⁴ reported that the number of house dust mites is associated with the onset of a respiratory allergy, especially bronchial asthma, and that there exists a threshold of house dust mite exposure to induce symptoms of asthma. Witteman et al. demonstrated that the exposure to an allergen such as *Der p.* can reduce FEV₁.²⁵ However, reports on the threshold of allergen-specific IgE to reduce pulmonary function are lacking in Korea.

The present study was undertaken to investigate a possible association of the reduction of pulmonary function with specific IgE values of four allergens, considered to be crucial inhalant allergens, such as house dust mites *Der p.* and *Der f.*, cockroach (a more harmful factor for the onset of asthma),^{26,27} and *Alternaria*, an important inhalant allergen that can be found throughout the year because of its prevalence regardless of season.

It is known that asthmatic children show more reduced FEV₁, FEV₁/FVC, and FEF_{25–75} values, even in the absence of an asthmatic attack, than do normal children.¹² The current study found significantly reduced FEV₁, FEV₁/FVC, and FEF_{25–75} values in the asthmatic group, even in stable status, than in the control group.

When positive rates of allergen-specific IgE between the asthmatic and control groups were compared, there were significant differences in the two house dust mite species and cockroach, but no difference in *Alternaria*, between groups. The prevalence of cockroach allergy is reported as 17–41% in the US and 12.5% in Korea;²⁷ we showed a relatively low positive rate of 14% in the present study. The positive rate of *Alternaria* was reported to be

TABLE 3—Comparison of Allergen-Specific IgE Positive Rates Between Asthmatic Group and Control Group¹

Inhalant allergen	Asthmatic group (%), N = 55	Control group (%), N = 48
<i>Der p.</i>	40 (72.7)* (42.6 ± 32.0 KU _A /l)	24 (50) (25.6 ± 31.5 KU _A /l)
<i>Der f.</i>	39 (70.9)* (58.6 ± 37.3 KU _A /l)	24 (50) (36.3 ± 37.6 KU _A /l)
<i>Alternaria</i>	8 (14.5) (27.4 ± 24.1 KU _A /l)	5 (10.4) (9.1 ± 7.6 KU _A /l)
German cockroach	9 (16.4)* (1.5 ± 1.7 KU _A /l)	2 (4.2) (1.4 ± 0.3 KU _A /l)

¹*P*-values were calculated by Pearson chi-Square test. *Der p.*, *Dermatophagoides pteronyssinus*; *Der f.*, *Dermatophagoides farinae*. Parentheses express mean ± SD of specific IgE.

**P* < 0.05 vs. controls.

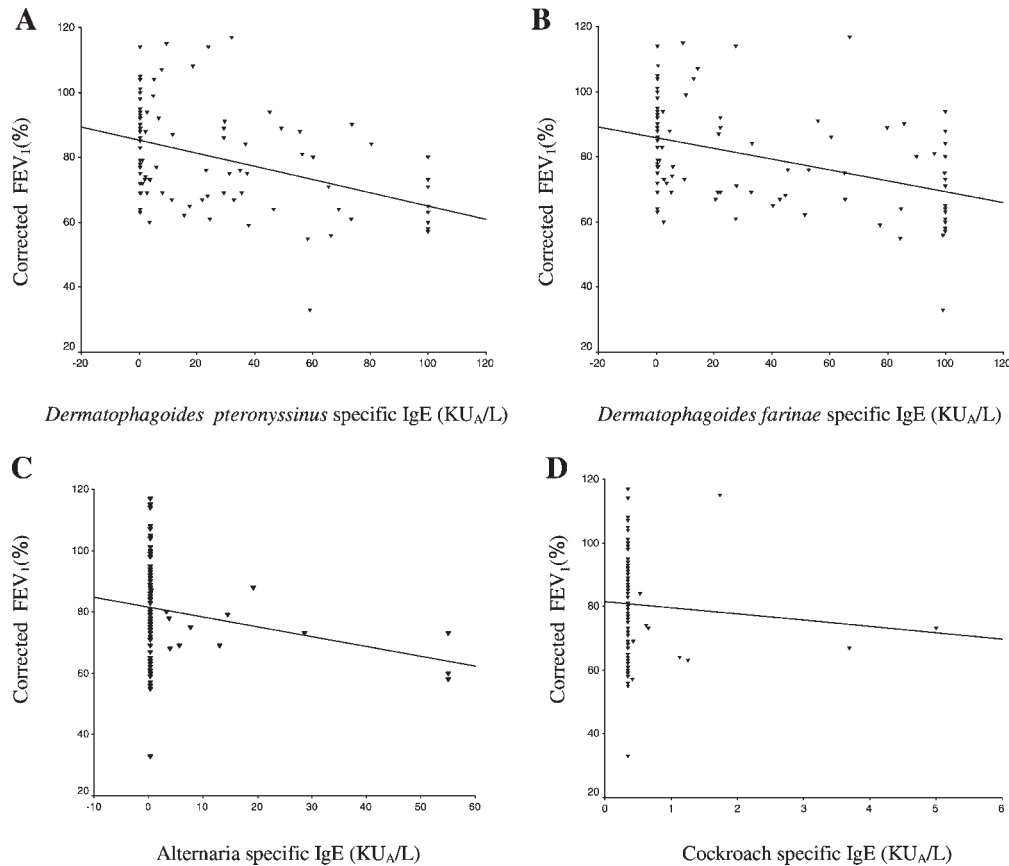


Fig. 1. Correlation between FEV₁ and allergen-specific IgE in asthmatic groups. A: Changes of FEV₁ related to *Dermatophagoides pteronyssinus*-specific IgE values. Correlation coefficient = -0.37 ($P < 0.05$). B: Changes of FEV₁ related to *Dermatophagoides farinae*-specific IgE values. Correlation coefficient = -0.44 ($P < 0.05$). C: Changes of FEV₁ related to *Alternaria*-specific IgE values. Correlation coefficient = -0.20 ($P > 0.05$). D: Changes of FEV₁ related to cockroach-specific IgE values. Correlation coefficient = -0.08 ($P > 0.05$). Correlation coefficients obtained by Pearson correlation.

10% on a skin test and 28% on a CAP system; however, it was 14.5% in the present study, without any significant difference between the two groups. The reasons for such results may be that a small number of subjects showed positive reactions due to a small number of total subjects, and that the sensitivity of the CAP system for *Alternaria* was as low as 57%, compared with 96% for house dust mites.²⁸

In reference to the relationship between specific IgE and pulmonary function in the asthmatic group, *Der f.* and *Der p.* showed statistically significant correlations with FEV₁ and FEF₂₅₋₇₅ on the pulmonary function test, and the other two allergens were also correlated with pulmonary function, but not with statistical significance. On the other hand, no correlation of any of the allergens was found in the control group.

Although constitutive rates of house dust mites found in Korea are somewhat different depending on the particular report, house dust mites constitute 50–97%, and *Der f.* and *Der p.* coexist such that *Der f.* is vastly dominant over *Der p.*, with some differences according to province.²⁹

More *Der f.* was found among house dust mites collected in Seoul, but *Der f.* and *Der p.* were simultaneously detected at 58.5%.³⁰ *Der p.*- and *Der f.*-specific IgEs were shown to have a very close cross-reaction with each other.^{13,31}

The present study also showed a significant connection between pulmonary function reduction and both *Der p.*- and *Der f.*-specific IgEs, which were particularly related to FEV₁ and FEF₂₅₋₇₅. This finding suggests that the cardinal affected site may be the narrow bronchus, with less than a 2-mm diameter in asthmatic children, as Hamid et al. reported.³² According to Lin et al.,¹³ FEF₂₅₋₇₅ seems to be associated with allergen-specific IgE more than the two other indices, FEV₁ and FEV₁/FVC.

Allergy skin prick tests for fungi revealed about 10% sensitization rates of all adults and children to various fungal allergens. In particular, *Alternaria* was shown to have the highest positive rate, which suggests that this fungus can be a causal allergen. A close correlation between the number of air-borne fungus spores, the seriousness of asthmatic symptoms, and the frequency of

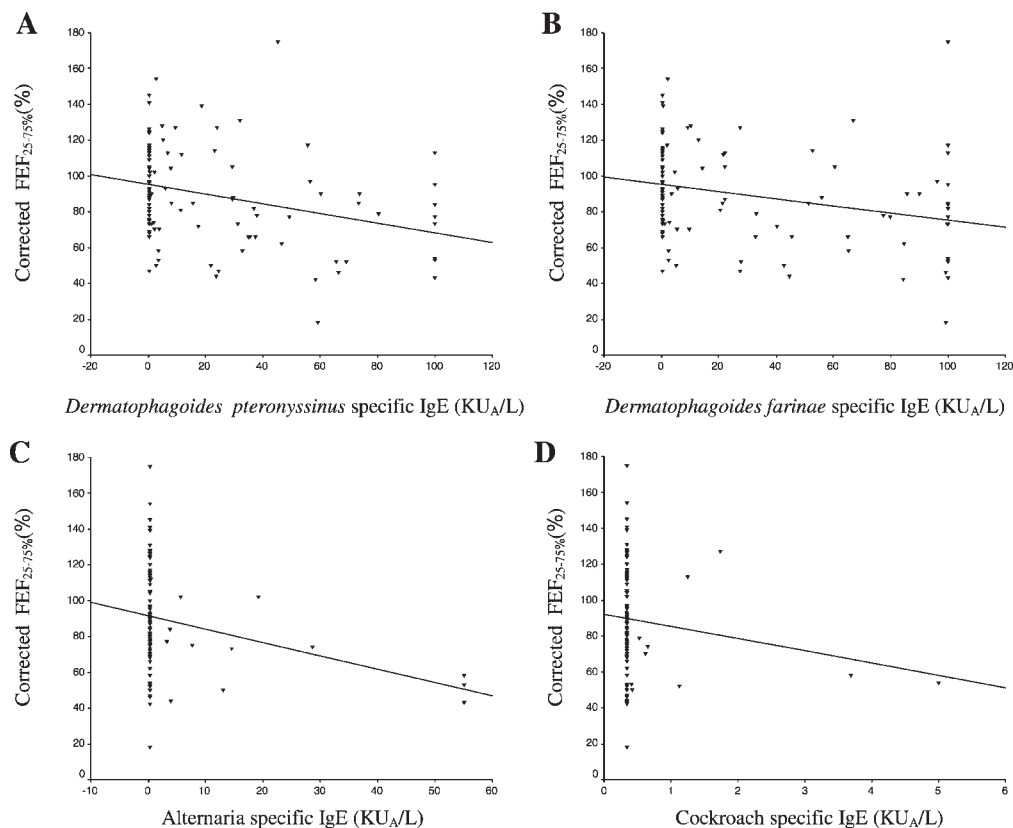


Fig. 2. Correlation between FEF_{25-75} and allergen-specific IgE in asthmatic groups. **A:** Changes of FEF_{25-75} related to *Dermatophagoides pteronyssinus*-specific IgE values. Correlation coefficient = -0.34 ($P < 0.05$). **B:** Changes of FEF_{25-75} related to *Dermatophagoides farinae*-specific IgE values. Correlation coefficient = -0.33 ($P < 0.05$). **C:** Changes of FEF_{25-75} related to *Alternaria*-specific IgE values. Correlation coefficient = -0.26 ($P > 0.05$). **D:** Changes of FEF_{25-75} related to cockroach-specific IgE values. Correlation coefficient = -0.18 ($P > 0.05$). Correlation coefficients were obtained by Pearson correlation.

asthma patients' admission to an emergency room was reported, and the number of spores in the atmosphere of Korea was found to be over the threshold which may induce symptoms. Therefore, fungi were suggested as an important causal allergen of asthma in the Korean environment.³³ However, in this study, *Alternaria* was found to have no statistically significant correlation with pulmonary function.

Since Kang et al.²⁶ reported an early and a late reaction followed by an inhalation challenge test of cockroach

extract, the cockroach allergen was suggested in numerous studies to be a prominent causal factor of asthma. However, in this study it was not found to be significantly correlated with pulmonary function. Because of the small total number of positive reactions, a precise detailed evaluation of *Alternaria*- and cockroach-specific IgEs in regard to their correlation with the pulmonary functions is difficult at present.

In conclusion, we measured four inhalant allergen-specific IgEs by employing the CAP system FEIA, and estimated pulmonary function in an asthmatic group and a control group, and the correlation between the value of each allergen-specific IgE and pulmonary function was investigated. The asthmatic group exhibited significant reduction in FEV_1 , FEV_1/FVC , and FEF_{25-75} compared with the control group. In particular, FEV_1 and FEF_{25-75} were statistically significantly reduced in relation to the IgE values specific to *Der p.* and *Der f.* among these inhalant allergens. Meanwhile, German cockroach and *Alternaria* allergens did not show a statistically significant correlation with reduced pulmonary function. No correlations were found in the control group. The above

TABLE 4—Pearman Correlation Coefficients, Calculated to Show Relationship Between Pulmonary Function and Allergen-Specific IgE in Asthmatic Patients

Variable	Corrected FEV_1	Corrected FEF_{25-75}	FEV_1/FVC
<i>Der p.</i>	-0.37^*	-0.34^*	-0.24
<i>Der f.</i>	-0.44^*	-0.33^*	-0.23
<i>Alternaria</i>	-0.20	-0.26	-0.49
German cockroach	-0.08	-0.18	0.15

* $P < 0.05$.

observations, therefore, suggest that *Der p*- and *Der f*-specific IgEs, and not German cockroach and *Alternaria*, may play a considerable role in reduced pulmonary function in asthmatic children.

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