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Usefulness of House Dust Mite Nasal Provocation Test in Asthma

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Purpose: We previously reported that the skin prick test was sensitive and the serum specific immunoglobulin E test was specific for predicting positive airway responses to house dust mites (HDMs) in patients with asthma. Because the nose and bronchus are one airway, the nasal provocation test would be more specific for predicting the bronchial responses to HDM than the skin test. **Methods:** The allergy skin prick test and nasal and bronchial provocation tests using HDM (*Dermatophagoides farinae*) were performed in 41 young men (age, 19-28 years) who wanted military certification for asthma. The nasal responses to HDM was scored according to the severity of rhinorrhea, sneezing, and nose itching. **Results:** The prevalence of a positive skin prick test to HDM did not significantly differ between patients with (n=24) and without (n=17) an early airway reaction (EAR; 79.2% vs 70.6%, P=0.534). However, the prevalence of a positive nasal test was significantly higher in the airway responders than in the others (37.5% vs 0%, P=0.005). The concordance of a positive response to the nasal test (κ=0.332, P=0.004) but not to the skin prick test (κ=0.091, P=0.529) was significant with an EAR. The diagnostic sensitivity of the nasal test (37.5%) was lower than that of the skin prick test (79.2%), but the specificity was higher (100% vs 29.4%). **Conclusions:** The skin prick test is more sensitive, whereas the nasal test is more specific and accurate, for predicting an EAR to HDM in patients with asthma.

Key Words: Asthma; *Dermatophagoides farinae*; nasal provocation test

INTRODUCTION

House dust mites (HDMs) are the most common inhalant allergens.[1] The relative risk for asthma symptoms and airway hyper-responsiveness (AHR) in HDM-sensitive children is 6.71.[2] The concentrations of, and sensitization rates to, HDM allergens are higher in autumn than in summer,[3] and exercise-induced asthma is highly prevalent and more severe in winter in accordance with the more frequent and severe sensitization to HDM in winter than in summer.[4]

The skin prick-puncture test is generally used to find a causative allergen because it is inexpensive and produces rapid results. However, we previously reported that the sensitivity of the skin prick test was higher than that of a serum specific immunoglobulin E (IgE) test for predicting a positive bronchial response to HDMs in patients with asthma, whereas the specificity of the IgE test was higher than that of the skin prick test.[5] Pastorello *et al.*[6] also showed that serum specific IgE antibody levels have greater diagnostic value for symptomatic allergies than the skin test.

The nose and bronchus are one airway, so a similar allergic reaction to the same allergen may occur simultaneously in the nose and bronchus.[7] In addition, provocation by a nasal allergen induces inflammatory mediators in bronchial mucosa and sputum,[8] and intranasal steroid treatment reduces asthma symptoms[9] and the risk for an emergency room visit due to an asthma attack.[10] Moreover, provoking segmental bronchi with an allergen induces nasal eosinophilic inflammation.[11] Therefore, the nasal provocation test may reflect a bronchial allergy more accurately than the skin prick test. However, no study has compared the value of the nasal test with the skin prick test for diagnosing a bronchial allergic reaction, and so this study was performed.

MATERIALS AND METHODS

Study subjects

Forty-one young men (age, 19-28 years old) who visited our hospital between February 2011 and January 2016 to obtain military certification for asthma underwent several challenge tests. They received a skin prick test using common aeroaller-

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gens, including the *D. farinae*, and a methacholine bronchial challenge test. They also underwent a nasal provocation test using *D. farinae* and histamine. The next day, an allergen inhalation challenge was performed with *D. farinae*. These and other demographic and laboratory data were collected from the participants' charts retrospectively. This study was approved by the institutional review board of our hospital (IRB No. CNUH-2016-156).

Methods

Before the tests, the subjects discontinued their medications for ≥1 week. The skin prick test was performed as previously described.[5] Briefly, 29 common aeroallergens, including the HDMs *D. pteronyssinus* and *D. farinae* (50,000 BU/mL; Allergopharma, Reinbek, Germany) were used. A histamine solution (1 mg/mL) and normal saline were used as positive and negative controls, respectively. Skin reactivity was categorized as follows, according to the ratio of the size of the allergen-induced wheal to the size of a wheal elicited by histamine: 1+, 25%-49%; 2+, 50%-99%; 3+, 100%-199%; and 4+, ≥200%. A clinically significant positive response was defined as ≥3+.[12] An elevated eosinophil level (eosinophilia) was defined as ≥450/μL,[13] and serum levels of IgE (normal <100 IU/mL) were measured using a nephelometer (Behring Diagnostics GmbH, Frankfurt, Germany).

Lung function tests were conducted using a computerized spirometer (Spiro-Analyzer ST-250; Fukuda Sangyo, Tokyo, Japan), and the regression equations described by Crapo *et al.*[14] were used to determine predicted values of forced expiatory volume in 1 second (FEV1). A bronchial challenge test was performed as previously described.[4,5] Briefly, freshly prepared methacholine solutions at concentrations of 0.075, 0.15, 0.31, 1.25, 2.5, 5.0, 10, and 25 mg/mL were aerosolized using a jet nebulizer (DeVilbiss 646; DeVilbiss Co, Somerset, PA, USA, output 0.13 mL/min) and inhaled by tidal breathing for 2 minutes at 5-minute intervals. The concentration that decreased FEV1 by 20% (PC20, mg/mL) was obtained using the linear interpolation method of the log dose-response curve. The *D. farinae* group I allergen (18 μg/mg; Yonsei University, Seoul, Korea) was diluted with phosphate-buffered saline (PBS; 1:1, 1:10, 1:30, 1:100, and 1:300) and inhaled by tidal breathing for 2 minutes at 30-minute intervals. An early airway reaction (EAR) or a late airway reaction (LAR) was defined as a ≥20% decrease in FEV1 within 1 hour or 3-24 hours after the last inhalation, respectively.

The nasal challenge test was performed using an empty nasal spray bottle (Nasacort AQ®, Sanofi-Aventis, NJ, USA). One spray delivered 0.1 mL. After checking the baseline, PBS and *D. farinae* solutions of 1:100, 1:10, and 1:1 were applied, in that order, through one spray in each nostril at 10 minutes intervals. Then the values of another baseline, post-PBS, and post-histamine solutions of 1.0, 4.0, and 16.0 mg/mL, which were applied in the same way as the allergen nasal challenge, were measured to assess nasal hyper-responsiveness to histamine. Nasal symptoms (rhinorrhea, sneezing, and nose itching) were scored for each challenge as follows: 0: none; 1: mild/moderate; and 2: severe. Thus, the maximum total nasal symptom score was 6. Before the challenge, 10 patients had nasal symptoms, including stuffiness, so the nasal test symptom score was calculated as the post-challenge score minus the basal score. When the stuffiness score was added to the test symptom score, the difference in the scores between patients with and without an EAR was statistically nonsignificant. Considering the total duration of the tests, the 10-minute intervals for the repeated challenges were relatively too short to check the late-phase reaction nasal stuffiness. In the same context, although we tried to measure nasal cavity diameter using an acoustic rhinometry system, the test results, which may be related to stuffiness, were inconsistent. Therefore, we excluded the stuffiness symptom score and rhinometric data from the analysis.

Statistical analysis

Data are expressed as means±standard error. Statistical analyses were performed using SPSS for Windows ver. 21.0 (SPSS Inc., Chicago, IL, USA). Comparisons between groups were made using Student's *t* test, the χ^2 test for a trend (linear-by-linear association), and Fisher's exact test. Correlations between individual variables were determined using Spearman's rank correlation coefficient analysis. The concordance of the tests was examined using kappa values. A *P* value <0.05 was considered significant.

RESULTS

Comparisons between the groups classified according to the bronchial challenge responses to the HDM *D. farinae*

Of the 41 patients, 24 (58.5%) showed a positive EAR to the HDM *D. farinae* inhalation challenge (Table 1). A LAR was not measured in 1 patient, and 13 (32.5%) of the remaining 40 patients had a positive LAR (11 dual responses and 2 isolated LARs). Overall, 26 (63.4%) patients had a positive EAR or LAR response to the allergen.

Age, blood eosinophilia, and increased serum levels of total IgE did not differ between the patients with and without an EAR. However, the baseline FEV1 values for the allergen bronchial provocation test were significantly lower in patients with an EAR than in those without an EAR. Although the prevalence of methacholine PC20 values in the so-called "asthmatic range" also tended to be higher in patients with an EAR, the difference was not significant. The average nasal challenge test score, but not the average skin prick test score, to *D. farinae* was significantly higher in patients with an EAR (Table 1). The proportion of subjects with a positive response to the nasal challenge test (37.5% vs 0%, *P*=0.005), but not to the skin prick test (79.2% vs 70.6%, *P*=0.534), with *D. farinae* was significantly higher in patients with an EAR (Figure). The prevalence of a history or evi-

Table 1. The clinical characteristics of young male asthma patients classified according to the responses to bronchial challenge test using *Dermatophagoides farinae*

	Overall		Early airway reaction		Late airway reaction	
	Negative (n=15)	Positive (n=26)	Negative (n=17)	Positive (n=24)	Negative (n=27)	Positive (n=13)
Age (year)	20.5±0.4	21.1±0.4	20.5±0.3	21.2±0.4	21.1±0.4	20.5±0.2
Current allergic rhinitis	2 (13.3%)	8 (30.8%)	2 (11.8%)	8 (33.3%)	7 (25.9%)	3 (23.1%)
Blood eosinophils ≥450/μL	4 (26.7%)	6 (23.1%)	4 (23.5%)	6 (25.0%)	8 (29.6%)	2 (15.4%)
Serum total IgE >100 IU/mL	11 (73.3%)	24 (92.3%)	13 (76.5%)	22 (91.7%)	22 (81.5%)	13 (100%)
FEV1, % predicted	89.8±3.9	81.9±2.1	90.0±3.5	81.1±2.2*	85.3±2.8	84.2±2.6
Methacholine PC20 <8 mg/mL	7 (46.7%)	20 (76.9%)	9 (52.9%)	18 (75.0%)	17 (63.0%)	9 (69.2%)
Skin prick test score to Df	2.73±0.41	3.35±0.23	2.88±0.37	3.29±0.25	2.96±0.28	3.38±0.33
Nasal test score to histamine	3.07±0.21	4.08±0.25†	3.35±0.27	3.96±0.26	3.63±0.23	3.92±0.38
Nasal test score to Df	0.20±0.11	0.88±0.22†	0.18±0.10	0.96±0.24†	0.78±0.21	0.38±0.21

FEV1, forced expiratory volume in 1 second; PC20; provocative concentration of methacholine resulting in 20% fall in FEV1; Skin prick test score (0-4) graded according to the ratio of the size of *Dermatophagoides farinae* (Df)-induced wheal to the size of the wheal elicited by 1 mg/mL histamine solution. Nasal test score graded according to the severity (0-2) of 3 nose symptoms (rhinorrhea, sneezing, and nose itching).
*P<0.05 and †P<0.01 compared to negative responder.

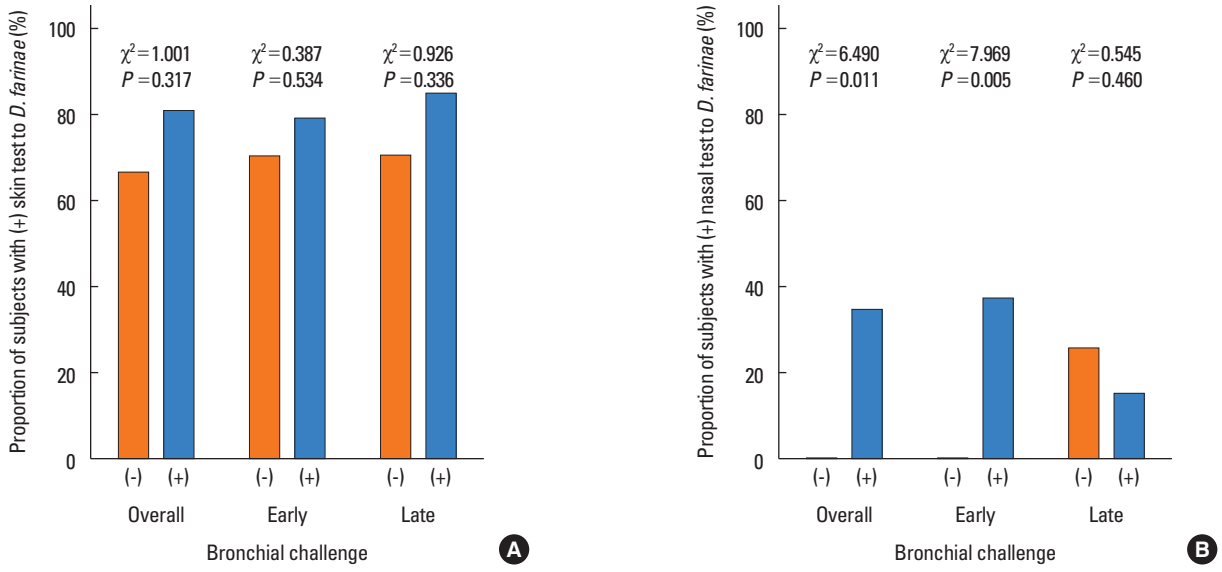

Figure. Comparison of the proportion of asthmatic subjects with a positive skin prick test response (≥100% of *Dermatophagoides farinae*/histamine wheal size ratio in prick test; left panel) and that with a positive nasal test response (≥2 of severity score grading to 0-2 of rhinorrhea, sneezing, and nose itching, respectively; right panel) between absence and presence of early or late airway reaction to *D. farinae* inhalation challenge.

dence of allergic rhinitis did not differ between patients with an EAR and those without an EAR (87.5% vs 100%, P=0.254). Patients with an EAR tended to have an increased prevalence of current allergic rhinitis (33.3% vs 11.8%, P=0.152; Table 1), and patients with current allergic rhinitis tended to show a positive nasal response to HDM more frequently (50.0% vs 29.0%, P=0.230).

None of the measured values differed between patients with and without a LAR (Table 1 and Figure). Overall, the nasal test, but not the skin prick test, showed significant differences in symptom scores and the percentage of responders to *D. farinae* between patients with and without an EAR or a LAR.

Relationship between the maximal fall in forced expiratory volume in 1 second during the early airway reaction to *Dermatophagoides farinae* and other variables

The maximal fall in FEV1 during an EAR to *D. farinae* was significantly correlated with the nasal test score, but not with the skin prick test score (Table 2). In addition, it was also significantly inversely related with FEV1 and the methacholine-PC20 value. The nasal test score was not significantly associated with other variables, including the skin prick test score.

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Table 2. Correlation coefficients between the maximal fall in forced expiratory volume in 1 second during the early airway reaction or nasal test score to *Dermatophagoides farinae* and other variables

	Blood eosinophils, %	Serum total IgE, IU/mL	FEV1, % predicted	Methacholine PC20, mg/mL	Skin prick test score to Df	Nasal test score to histamine	Nasal test score to Df
Early airway reaction	0.219	0.109	-0.428†	-0.357*	0.149	0.204	0.380*
Nasal test score to Df	0.109	0.176	-0.285	-0.197	0.067	-0.004	-

FEV1, forced expiratory volume in one second; PC20, provocative concentration of methacholine resulting in 20% fall in FEV1; Skin prick test score (0-4) graded according to the ratio of the size of *Dermatophagoides farinae* (Df)-induced wheal to the size of the wheal elicited by 1 mg/mL histamine solution. Nasal test score graded according to the severity (0-2) of 3 nose symptoms (rhinorrhea, sneezing, and nose itching).
*$P<0.05$; †$P<0.01$.

Table 3. The concordance of the positive bronchial response to house dust mite *Dermatophagoides farinae* with the positive skin prick or nasal test response to *D. farinae*

		Overall				Early airway reaction				Late airway reaction			
		(-)	(+)	κ value	*P* value	(-)	(+)	κ value	*P* value	(-)	(+)	κ value	*P* value
Skin test	(-)	5	5	0.152	0.311	5	5	0.091	0.529	8	2	0.106	0.330
	(+)	10	21			12	19			19	11		
Nasal test	(-)	15	17	0.279	0.010	17	15	0.332	0.004	20	11	-0.115	0.455
	(+)	0	9			0	9			7	2		

Skin prick test positive: ≥100% of *Dermatophagoides farinae*/histamine wheal size ratio in prick test. Nasal test positive: ≥2 nasal score graded according to the severity (0–2) of 3 nose symptoms (rhinorrhea, sneezing, and nose itching).

Table 4. The diagnostic sensitivity, specificity, and accuracy of skin prick or nasal test to Dermatophagoides farinae based on a positive response to bronchial challenge test to *D. farinae*

	Overall			Early airway reaction			Late airway reaction		
	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy
Skin prick test									
≥2+	92.3	20.0	65.9	91.7	17.6	61.0	92.3	14.8	40.0
≥3+	80.8	33.3	63.4	79.2	29.4	58.5	84.6	29.6	47.5
4+	69.2	53.3	63.4	66.7	47.1	58.5	69.2	44.4	52.5
Nasal provocation test									
≥1	42.3	80.0	56.1	45.8	82.4	61.0	23.1	59.3	47.5
≥2	34.6	100	58.5	37.5	100	63.4	15.4	74.1	55.0
≥3	11.5	100	43.9	12.5	100	48.8	0	88.9	60.0

All values are expressed as %.
Skin test grading: 2+: 50%-100%, 3+: 100%-200%, 4+: ≥200% of *Dermatophagoides farinae*/histamine wheal size ratio in prick test. Nasal test grading according to the severity (0-2) of 3 nose symptoms (rhinorrhea, sneezing, and nose itching).

Concordance of the bronchus and skin or nose test results with sensitivity to *Dermatophagoides farinae*

All patients with a positive response in the nasal test showed a positive EAR to *D. farinae* (Table 3). Only 2 patients with a positive nasal test showed a positive LAR, but all patients with a positive nasal test had a bronchial EAR or LAR. Therefore, the concordance of the nasal test response and an EAR (κ=0.332, $P=0.004$), but not a LAR, was significant. However, only 19 of 31 patients with a significant positive response to the skin prick test showed a positive an EAR to *D. farinae*; thus, the concordance of the skin prick test response and an EAR was not significant (κ=0.091, $P=0.529$).

Diagnostic sensitivity, specificity, and accuracy of the tests

The diagnostic sensitivity, specificity, and accuracy of the tests to airway reactions at the various cutoff values are presented in Table 4. The accuracy of the skin prick test was highest at a cutoff value of ≥2+ for an EAR, but at 4+ for a LAR. The accuracy of the nasal provocation test was highest at a cutoff value of ≥2 for an EAR, but at ≥3 for a LAR. When a cutoff value of ≥3+ for

the skin prick test, which is generally considered a clinically significant response,[12] and ≥2 for the nasal test were applied, the sensitivity of the skin prick test (79.2%) for an EAR was higher than that of the nasal test (37.5%); the opposite was true for specificity (29.4% vs 100%). Even at a cutoff value ≥1, the sensitivity of the nasal test was lower than that of the skin prick test, whereas the specificity of the skin prick test was lower than that of the nasal test even at a cutoff value of 4+.

Similarly, the sensitivity of the skin prick test for a LAR was higher (84.6% vs 15.4%), but specificity (29.6% vs 74.1%) was lower, than that of the nasal test (Table 4). The sensitivity of the nasal test at a cutoff value ≥1 for a LAR was lower than that of the skin prick test, and the specificity of the skin prick test at a cutoff value of 4+ was lower than that of the nasal test. The accuracy of both the skin and nose tests for a LAR tended to be lower than that for an EAR.

DISCUSSION

We found that the skin prick test was more sensitive, whereas the nasal provocation test was more specific, for predicting an EAR to *D. farinae* in patients with asthma. This result is similar to that of our previous report showing that the skin prick test is sensitive and that the *D. farinae*-specific serum IgE test is specific.[5] Because allergen-specific serum levels of IgE for certain foods above the diagnostic cutoff values are highly predictive of food allergy, the serum IgE test can eliminate the need to perform double-blind, placebo-controlled food challenges.[15] Similarly, the nasal test at a cutoff value ≥2 showed 100% specificity for an EAR in the present study, so this very simple safe test may replace the very difficult inhalation challenge for patients with asthma.

Although we did not directly compare the diagnostic values of the nasal test and the *D. farinae*-specific serum IgE test, the specificities of the IgE test at cutoff values ≥ class 4 and of class 6 for an EAR were 71.4% and 95.2%, respectively, in our previous study.[5] Because the diagnostic decision level of food-specific serum IgE is above a value at which patients are >95% likely to experience a food allergy,[16] the diagnostic decision level of *D. farinae*-specific serum IgE for an EAR in patients with asthma was class 6, which is the highest class. However, the specificity of the nasal test in the present study was 100% at a cutoff value ≥2, so the diagnostic decision level of the nasal test for an EAR in patients with asthma was only 2 of the maximum 6. Therefore, the nasal test is more highly specific than the serum IgE test, and it may be used as a confirmatory test instead of the inhalation challenge.

The microenvironment in the blood, including *D. farinae*-specific serum IgE antibodies, may be more intimately related with the lower airways compared to that in the skin, an organ distant from the airways.[5] In the same way, the nose and bronchus are one airway, so the nose may reflect the lower airway much more accurately than does the skin. Actually, the concordance of the positive nasal test (cutoff value ≥2), but not the positive skin prick test (cutoff value ≥3+), with the positive bronchial response was significant in the present study. In addition, the nasal test score, but not the skin prick test score, was significantly correlated with the maximal fall in FEV1 during an EAR, and the nasal test score, but not the skin prick test score, was significantly higher in patients with an EAR than those without it.

Because the same allergens are inhaled through the nose into the bronchi, similar allergic reactions may occur concomitantly in both organs.[7] Of course, allergic reactions in the upper and lower airways do not always occur together. Asthma occurs in only 13.4% of patients with perennial rhinitis; however, more than 75% of patients with allergic asthma have accompanying rhinitis[17] and 84% of asthmatics respond to a nasal allergen challenge even if they have no rhinitis symptoms.[18] Several mechanisms for the effects of rhinitis on asthma have been proposed, including the same mediators, post-nasal drip, nasobronchial reflex, and mouth breathing secondary to a nasal obstruction.[17] Moreover, Braunstahl *et al.*[11] showed that segmental bronchial provocation with an allergen results in nasal eosinophilic inflammation and rhinitis symptoms, although Xie *et al.*[19] failed to find a similar reaction in a mouse model. Therefore, we speculate that the nose reflects the bronchus very well.

Cockcroft *et al.*[20] and Sicherer *et al.*[21] showed that an EAR to an allergen was significantly related to AHR, which is consistent with our results. Although sensitization to HDMs is an important risk factor for asthma,[2] only a small fraction of sensitized individuals develops asthma.[17] Therefore, an EAR to HDM *D. farinae* was not significantly related with skin prick test reactivity to *D. farinae* in the present study. In the same way, a positive nasal response to *D. farinae* may not always predict an EAR. Sicherer *et al.*[21] reported that nasal responses to tests in a cat-exposure room or using allergen-soaked disks were not significantly related with an EAR to the environmental or nasal challenge to cats. However, all patients with a positive nasal response (≥2) to *D. farinae* in the present study showed an EAR to *D. farinae*, and the nasal symptom scores were significantly correlated with the maximal fall in FEV1 during an EAR. This discrepancy may be explained, at least in part, by the difference in subject characteristics. The subjects in Sicherer *et al.*[21] included patients with rhinitis without asthma, but all of our subjects had suspected asthma although some patients showed a negative methacholine-AHR. Of course, patients with current allergic rhinitis may more frequently respond to both nasal and bronchial challenge with HDM, although such a trend only was found in the present study. Other authors[22-24] have previously reported the diagnostic value of the nasal provocation test with allergens in patients with asthma, but they did not investigate the relationship between the allergen responses between the nose and bronchus. Therefore, the present study is the first to show the usefulness of the

nasal test to find etiologic agents of asthma.

The LAR is associated with marked eosinophilic airway inflammation and prolonged AHR, and so it is clinically more important than the EAR.[25] However, both the skin prick and nasal challenge tests in the present study determined the immediate allergic reaction to *D. farinae* as a positive reaction in the skin and nose, respectively. Such tests to detect immediate allergic reactions in the skin and nose may not reflect LAR very well, as shown in the present results. Further studies using tests for late allergic reactions in the skin and nose are required to predict LAR. In addition, artificially inducing allergic reactions in the nose and bronchus with a nasal spray and nebulizer may not accurately reflect the natural reactions. Environmental challenge in an exposure room would be better than our method, but the relationship between the results by the methods was highly significant in Sicherer *et al*.[21]

In summary, the skin prick test was more sensitive, whereas the nasal provocation test was more specific and accurate, for predicting an EAR to *D. farinae* in patients with asthma.

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