
Prick puncture skin tests and serum specific IgE as predictors of nasal challenge response to *Dermatophagoides pteronyssinus* in older adults

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Background: The ability of prick puncture skin test (PPST) results and the presence of serum specific IgE (sIgE) to *Dermatophagoides pteronyssinus* to predict positive or negative nasal challenge (NC) results has not been determined in older adults.

Objective: To determine if allergy skin test and/or serum sIgE is diagnostic of allergic rhinitis in older adults.

Methods: Forty-eight adults (20 younger and 28 older) with rhinitis underwent NC to *D pteronyssinus* 1 to 4 weeks after PPST and sIgE to *D pteronyssinus*. Patients were not aware of their in vivo or in vitro results at the time of their NC.

Results: Fourteen of 48 adults (10 younger and 4 older) were NC positive. The positive predictive values for older adults with positive NC results ranged from 28.57% to 42.86% for PPST and was 16.67% for sIgE. In contrast, positive predictive values in younger adults ranged from 76.92% to 100% for PPST and was 100% for sIgE. However, negative PPST results and sIgE had high predictive values for a negative NC result to *D pteronyssinus* in older adults (90.48%–95.24% for PPST and 89.47% for sIgE).

Conclusions: Although PPST and sIgE negative results were good predictors of negative NC outcomes, neither positive PPST results nor serum sIgE to *D pteronyssinus* predicted positive NC results in older adults. PPST and sIgE to *D pteronyssinus* were excellent predictors of both positive and negative NC outcomes in younger adults.

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INTRODUCTION

The ability of prick puncture skin test (PPST) and serum specific IgE (sIgE) to *Dermatophagoides pteronyssinus* to predict positive or negative nasal challenge (NC) results has not been established in older adults (>60 years). In addition, few data are available regarding the prevalence or course of allergic rhinitis in elderly patients.¹ Although a few studies have compared the results of dust mite NC to sIgE or PPST to dust mite, no studies have directly compared the difference of these results between older and younger adults. To our knowledge, only 2 studies of perennial allergic rhinitis with NC including individuals older than 60 years have been published.^{2,3} Because of the lack of data comparing PPST and sIgE to NC responses in elderly patients, this study was designed to determine if allergy skin test and/or sIgE is diagnostic of allergic rhinitis in older adults. Specific aims were to compare the performance characteristics (sensitivity, specificity, and predictive values) of skin tests and sIgE to *D*

pteronyssinus, using NC response as a gold standard, in diagnosing nasal allergy to *D pteronyssinus* in younger and older patients and to compare sIgE to PPST response in younger and older patients.

METHODS

Study participants were recruited following standard guidelines for human clinical trials. All participants received a full explanation of the study and signed an informed consent before participating in the study. The University of South Florida and James A. Haley Veterans Hospital institutional review boards approved the study protocol.

Inclusion criteria included a suspected clinical diagnosis of perennial allergic rhinitis, with or without allergic asthma, and an age of 60 years or older at referral time for the older group and 20 to 59 years for the younger group. Patients with perennial rhinitis had symptoms during most of the year for at least 1 year. Perennial rhinitis was not further classified.

Exclusion criteria included skin disease or scars in the area of skin tests; use of β -blockers; any cigarette smoking in the last year; systemic diseases, including infectious, metabolic, connective tissue, cystic fibrosis, or malignancy within the past year; pregnant or lactating women; history of nude sunbathing or tanning parlor exposure for more than 30 days in a lifetime or any time in the past year; allergen immunotherapy within the last year; and antihistamine or nasal medication use within the week before NC. Participants who, on physical examination, had nasal polyps, sinusitis, or any anatomical abnormalities or current infection of the upper

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airway were also excluded. Forced expiratory volume at 1 second (FEV₁) was measured before each NC and before leaving the clinical research unit. An FEV₁ of 70% predicted was required to proceed to the next NC.

Twenty-eight older (mean age, 67.8 years; 11 women and 17 men) and 20 younger (mean age, 34.1 years; 14 women and 6 men) individuals with a provisional clinical diagnosis of allergic rhinitis were recruited from patients referred to the James A. Haley Veterans' Hospital and private allergy clinics in Tampa, Florida. Long-acting antihistamines and other medications known to affect the allergy skin test response were withheld 7 or more days before PPST. All intranasal medications were withheld 7 or more days before NC. One to 4 weeks before NC, all study participants underwent PPST to 5 common local allergens, which included standardized *D pteronyssinus* (10,000 AU/mL), German and American cockroach mix, cat hair, oak mix, and short ragweed (Greer Laboratories, Lenore, North Carolina). All PPSTs and NCs were performed between November 1, 1998, and September 31, 2000. PPSTs were performed with a Morrow Brown needle (Alkaline Corporation, Oakhurst, New Jersey) using glycerinated phenol saline (negative) and histamine (positive) controls (histamine base, 1.8 mg/mL) on the upper back. Response measurements were recorded as mean wheal diameter minus the reaction to the diluents. Cutoff levels for positive PPST results were wheals of 3 mm, 5 mm, or histamine equivalent prick (HEP) (ratio of allergen wheal to histamine control wheal ≥ 1.0). Three cutoff levels were selected to determine which level was most efficient in predicting NC response.

Blood samples were obtained before NC from 44 of 48 participant (4 individuals either declined venipuncture or venipuncture was unsuccessful), and serum samples were sent to the immunology laboratory at the National Institute for Occupational Safety and Health (NIOSH) (Morgantown, West Virginia) for assay of sIgE to *D pteronyssinus* using the Pharmacia system (Pharmacia Diagnostics, Uppsala, Sweden). Results were reported as kilounits of allergen per liter (kUA/L) for allergen sIgE as previously described.⁴ A positive test result was defined as an sIgE level of 0.35 kUA/L or greater.

All study participants were blinded to *D pteronyssinus* and sIgE skin test results before NC. No participants had symptoms other than itching at the time of their skin tests. Participants were not told which skin test results, if any, were positive until after NC was completed. Study personnel were not blinded but were properly trained and instructed to follow the study procedures before NC to eliminate potential bias due to the influence on the responses of study participants to the symptom scoring. A positive NC result was defined as a doubling of symptom scores to a minimum postchallenge score of 10, peak nasal inspiratory flow (PNIF) decline of 50% or greater, or failure to return to within 20% of baseline PNIF after challenge. Doubling of symptom scores and a minimum score of 10 were selected after reviewing the literature and talking with experts in NC. The inclusion of the

younger participants as a control group served as a within-study control.

Baseline PNIF and symptom scores were recorded after the participants had time to adjust to the indoor climate and before NC with phosphate-buffered saline. They were recorded every 10 minutes until the PNIF was within 20% of the last 2 measurements. The NC was performed by placing 0.1 mL of phosphate-buffered saline bilaterally on the inferior nasal turbinates via syringe without a needle, followed by 0.1 mL of *D pteronyssinus* (10, 100, and 1,000 AU/mL, sequentially) at 30-minute intervals. If more than a 20% decline in PNIF occurred, the subsequent challenge was delayed until a return to within 20% of baseline. If a patient's PNIF failed to return to within 20% of baseline within 1 hour, further challenge was not performed. PNIF was measured using the method described in the package insert for In-Check Nasal Inspiratory Flow Meter (Clement Clarke, Harlow, England).⁵

Symptom scores were graded on a 0 to 3 scale (0 indicating no symptoms; 1, mild symptoms; 2, moderate symptoms; and 3, severe symptoms) for each of the following: runny nose, nasal congestion, sneezing, itchy nose, itchy/gritty eyes, runny/watery eyes, red/burning eyes, and ear/palate itch. Results were combined for a maximum score of 24. Participants were asked to call the clinical research unit if they had any delayed symptoms. Only 1 participant called: a 65-year-old who had mild bronchospasm.

Standard statistical data analysis methods and techniques were used to estimate the effectiveness of different diagnostic tests in predicting NC results in the elderly group. NC was used as a gold standard test to evaluate the precision and accuracy of other diagnostic tests. The Spearman correlation analysis was performed to estimate the association among NC, sIgE, PPST, HEP, and mean corrected wheal to *D pteronyssinus* and outcomes for study participants. Contingency table analyses were used to calculate sensitivity, specificity, and predictive values for younger and older groups. Because of the small number of study participants in the 2 $\times$ 2 table analyses (fewer than 5 study participants in a single category), the Fisher exact test and corresponding *P* values for statistical significance were used instead of the χ^2 test. Sensitivity and specificity estimates were calculated to describe positive and negative predictive values of each selected test as compared with NC results. Statistical analysis was performed using the SAS System for Windows 8.02 statistical software package (SAS Institute Inc, Cary, North Carolina). Because no preliminary data were available to use in performing a power analysis before the study, 30 participants were recruited in each age group for the skin test portion of the study. All participants were invited to participate in the NC study; 20 of the younger patients and 28 of the older patients volunteered and qualified.

RESULTS

The NC result was positive in 14 of 48 study participants (10 in the younger group and 4 in the older group). Two partic-

ipants (1 older and 1 younger) had positive NC results at 10 AU/mL, 3 (1 older and 2 younger) at 100 AU/mL, and 9 (2 older and 7 younger) at 1,000 AU/mL. The results of the *D pteronyssinus* skin tests, sIgE tests, and NCs are summarized in Table 1. Thirteen study participants tested positive by PNIF, 8 by symptom scores, and 6 by both PNIF and symptom scores. Performance characteristics are summarized in Table 2.

Wheal sizes correlated with the percentage of PNIF decline in younger participants ($r = .79$; $P < .001$) but not older participants ($r = .35$; $P = .07$). In younger participants there was a trend toward decreased PNIF with increased sIgE levels ($r = .30$; $P = .054$) but not in older participants. Furthermore, a lower provocative dose of allergen correlated with increased sIgE levels in younger ($r = .81$; $P < .001$) but not in older participants ($r = .03$).

For younger participants, a HEP level of 1.0 or greater was the best PPST predictor of NC outcome. For older participants, a wheal of 3 mm or larger was the best PPST predictor, but the P value of a wheal of 3 mm or larger for older participants is marginal and should be used with extra caution for interpretation purposes ($P = .04$) (Table 2).

Serum sIgE was 100% accurate in predicting positive NC outcome in young people but had a small probability of predicting positive NC results in older people. Positive and negative predictive values of each diagnostic test are presented in Table 2. The highest positive predictive value was shown for specific IgE, HEP, and PPST of 5 mm in the younger group. The highest negative predictive values, as indicators of the best test to rule out the disease, were revealed for a PPST wheal smaller than 5 mm, an HEP value less than 1.0, and an sIgE level of less than 0.35 IU in younger people, whereas in the older people a PPST wheal of less than 3 mm was best.^{6,7}

Fifteen of the 28 older study participants tested negative to *D pteronyssinus* by all parameters (sIgE, HEP, PPST wheal <3 mm, and negative NC result). Results of the 13 older individuals with 1 or more positive test results to *D pteronyssinus* are summarized in Table 3.

DISCUSSION

The results suggest that skin tests and in vitro tests (sIgE) are not as useful in diagnosing perennial allergic rhinitis to *D pteronyssinus* in older patients as they are in younger patients. Both sIgE and PPST were exceptionally good predictors of NC outcome in younger participants as outlined in Table 2. Although statistical significance was limited by the sample size of the study population, the clinical importance of the findings comparing the efficacy of different tests in younger vs older study population groups is self-evident and cannot be overlooked. Specific IgE was perfect in predicting both positive and negative NC responses in 18 younger individuals; however, only a negative sIgE result predicted negative NC responses in older individuals (Table 2).

The strength of the association between the PPST and NC was statistically significant ($P < .01$) in the younger participants for all cutoff levels but only marginally statistically significant ($P = .04$) for the 3-mm wheal in older participants. The strength of association between sIgE and NC was only statistically significant for younger participants. The small number of positive NC results in older participants may influence positive predictive values and further interpretation of our study findings specific to older adults. Only 4 older individuals had a response that fit the criteria prospectively chosen for a positive NC result. Of these 4 individuals, only 2 had positive results predicted by skin test or sIgE. In contrast, in younger individuals serving as a control, all 10 positive NC results and all 10 negative NC results were predicted by skin test and/or sIgE. A PPST cutoff of 3 mm was less effective in the younger participants compared with the older participants. The older group of participants with allergic rhinitis revealed lower responsiveness to PPST of 5 mm, HEP, and sIgE compared with the younger group.

The results of the present study are supported by 2 previous studies.^{2,3} Reichelmann et al, in a retrospective study of 235 participants with a positive PPST result to *D pteronyssinus*, found that "quality and severity of symptoms, clinical history, skin tests and allergen-specific IgE determinations were un-

Table 1. Number of Nasal Challenges in Agreement With Prick Puncture Skin Tests and Serum Specific IgE

Nasal challenge result	<i>Dermatophagoides pteronyssinus</i> mean wheal diameter, mm			HEP ≥ 1.0	<i>D pteronyssinus</i> specific IgE, kUA/L	
	0-3	3-5	>5		<0.35	≥ 0.35
Younger group (n = 20)						
Negative	7	2	1	0	8	0 ^a
Positive	1	0	9	9	0	10
Older group (n = 28)						
Negative	16	4	4	5	17	5 ^a
Positive	1	1	2	2	2	1 ^b

Abbreviation: HEP, histamine equivalent prick.

^a Two study participants were not tested.

^b One study participant was not tested.

Table 2. Performance Characteristics of PPST and sIgE for Predicting Nasal Challenge Outcome to *Dermatophagoides pteronyssinus*

Characteristics	Sample size	PPV, %	NPV, %	Sensitivity, %	Specificity, %
Wheal ≥ 3 mm					
Younger ^a	20	76.92	100	70	100
Older ^b	28	42.86	95.24	75	83.33
Wheal ≥ 5 mm					
Younger ^c	20	90.91	100	100	90
Older	28	40.00	91.30	50	87.50
HEP ≥ 1					
Younger ^c	20	100	100	100	100
Older	28	28.57	90.48	50	79.17
sIgE					
Younger ^c	18	100	100	100	100
Older	25	16.67	89.47	33.33	77.27

Abbreviations: HEP, histamine equivalent prick; NPV, negative predictive value; PPST, prick puncture skin tests; PPV, positive predictive value; sIgE, specific IgE.

^a $P \leq .01$ of Fisher exact test for the strength of association between the diagnostic test and the gold standard nasal challenge.

^b $P \leq .05$ of Fisher exact test for the strength of association between the diagnostic test and the gold standard nasal challenge.

^c $P \leq .001$ of Fisher exact test for the strength of association between the diagnostic test and the gold standard nasal challenge.

Table 3. Characteristics and Values for Older Individuals With Any Positive Test Results to *Dermatophagoides pteronyssinus*^a

Age, y	Sex	Asthma	NC status	Specific IgE, kUA/L	Specific IgE class (range, 0–6)	Wheal mean diameter, mm	HEP	PNIF, % decrease	Symptom score before/after
60	M	Yes	Positive	ND	ND	12.5	3.6	59	5/12
61	F	Yes	Positive	0	0	1	0.2	50	8/4
61	F	No	Negative	ND	ND	3	0.9	0	11/14
61	M	Yes	Negative	6.82	3	5.5	1.1	20	1/1
64	M	Yes	Positive	0	0	4	0.7	20	6/13
65 ^b	M	Yes	Negative	ND	ND	16.5	3.0	10	1/3
66	M	No	Positive	5.57	3	14	5.6	63	2/11
66	M	No	Negative	1.48	2	3.5	0.7	6	2/0
68	M	No	Negative	<0.35	0	3.5	0.6	35	1/6
69	F	No	Negative	<0.35	0	5	0.8	7	3/1
70	M	No	Negative	0.41	1	2	0.5	25	6/5
70	M	Yes	Negative	36.6	4	25	5.6	24	0/3
73	F	Yes	Negative	1.53	2	9	1.3	11	3/8

Abbreviations: HEP, histamine equivalent prick; NC, nasal challenge; ND, not done; PNIF, peak nasal inspiratory flow.

^a Bold type indicates positive test result.

^b Bronchospasm 8 to 10 hours after challenge.

reliable predictors of the outcome of NC to *Dp* [*D pteronyssinus*].” The NC result was positive in 40% of all participants, and participants with negative NC results were older than those with positive NC results. In participants with positive skin test results, those younger than 40 years had more positive NC results, whereas those 40 years and older had more negative NC results. There were 8 individuals older than 60 years, of whom only 3 had positive NC results.

Twenty years after the start of their study, Simola et al reinterviewed 107 individuals 27 to 78 years old (mean age, 51 years) who had been skin tested and had undergone nasal provocation tests at baseline. Their current allergic rhinitis status was verified with PPST and NC. Skin test reactivity after 20 years showed a significant decrease with age overall for allergens (22 to 26 allergens). Of those individuals with any positive skin test results, a positive NC result was less

likely in older individuals (96% in those younger than 46 years, 70% in those 46 through 56 years, and 53% in those older than 56 years).

NC mimics natural exposure to allergen better than either skin or in vitro (sIgE) testing. Disadvantages of NC for perennial nasal allergens such as dust mites include the following: (1) persistent inflammation from natural exposure makes it difficult to establish baseline nasal function; (2) application of allergen during a short period, as opposed to chronic natural exposure over months to years; (3) the end points for PNIF must be stringent enough to avoid false-positive results by circadian or vasomotor variations in nasal flow; (4) symptom scores are highly subjective and can be biased by the investigator or the subject; and (5) late-phase reactions may be missed unless individuals are observed for 8 to 12 hours. PNIF was chosen because it is simple, inex-

pensive, reproducible, and, with the exception of study participant effort, objective. Symptom scores were also obtained because measurement of flow is not universally accepted. Ideally, both flow and symptom scores should change in a positive challenge result. Although some articles describe validation of specific methods (for example, PNIF), there are no universally accepted, validated methods for NC.

The workshop on Allergic Rhinitis and its Impact on Asthma suggests that NC may prove to be beneficial in difficult cases and/or as a confirmatory test before instituting allergen immunotherapy.⁸ After the data for the present study were obtained, PNIF as a nasal provocation method to house dust mite was validated in younger individuals.⁹ PNIF is easily adaptable to office or clinic use for confirmation of a clinical impression of nasal allergy to *D pteronyssinus*. It was chosen to measure NC outcome because it is inexpensive and reproducible, correlates well with rhinomanometry, and is easily performed by the study participant. Furthermore, PNIF is more sensitive to mucosal changes than other methods of measurement.¹⁰ One precaution in performing PNIF in older individuals is the possible occurrence of nasal wall collapse during rapid inhalation (nasal valve).

The results of this study raise important questions. First, do skin tests, sIgE, and NC measure different "pools" of IgE? It has been suggested that sIgE on skin mast cells and/or serum sIgE indicate sensitization but not necessarily clinical allergy.¹¹ It may be that the disparity between NC and skin tests or serum sIgE in older individuals represents loss of local, nasal *D pteronyssinus* sIgE. Other studies have demonstrated local production of sIgE in the nasal-associated lymphoid tissue.^{12–16} In cases in which skin tests and/or sIgE do not confirm a clinical impression of dust mite allergy, NC offers additional information. It is possible that the nose may have sIgE to *D pteronyssinus* that is not detected by skin test or sIgE in the serum.¹⁷ We were unable to find studies of sIgE or markers of IgE activity in the nasal mucosa of older humans. Discordance in omalizumab inhibition of allergen responses was noted; nasal provocation response and sIgE levels were rapidly decreased after omalizumab injections, but reduction of immediate skin test response to allergen was not noted for several weeks.^{18–20}

Second, do older individuals lose their ability to mount a positive NC result even though sIgE may be present in the nasal tissue? Rhinitis in elderly individuals was recently reviewed by Sahia-Yilmaz and Corey, who concluded that information about the effect of aging on nasal tissue is limited.¹ The few studies they referenced found that (1) human respiratory and olfactory mucosa has an age-related decrease in the intensity and extent of immunoreactivity within nasal cells²¹; (2) no significant age-related changes in gross or electron microscopy examination were found in nasal tissue²²; and (3) stratified epithelial types initially increase with age but decrease in those older than 50 years.²³ There were no references of IgE or markers of IgE activity in the nasal mucosa in elderly patients.

In conclusion, the present study suggests that nasal response to *D pteronyssinus* is less likely in older individuals and that neither skin test nor serum sIgE is sufficient evidence of nasal allergy in this age group. NC may be especially useful in older patients for confirming clinical allergy to *D pteronyssinus* when skin or in vitro test results are positive, especially before recommending expensive changes in the home environment or allergen immunotherapy. Likewise, in patients with symptoms of perennial rhinitis but with negative PPST results or sIgE to *D pteronyssinus*, NC may confirm local nasal allergy. Larger studies are needed of age-related changes in the sIgE activity in nasal mucosa and the ability of the aged nose to respond to allergy-related mediators, such as histamine.

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