



Comparison between skin prick test and serum immunoglobulin E by CAP system to inhalant allergens



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ABSTRACT

Background: Skin prick tests (SPTs) and measurements of serum specific immunoglobulin E (sIgE) antibodies are the most commonly used diagnostic tools for confirming sensitization. However, disagreement between the tests has been observed.

Objective: To compare SPT and the CAP system for diagnosis of sensitization to common inhalant allergens.

Methods: Subjects included 2,635 patients 10 to 90 years old who underwent analyses by SPT and CAP at the Dong-A University Hospital (Busan, Korea) from June 2011 through May 2016. The 2 test results were compared for 17 inhalant allergens.

Results: Agreement between the SPT and sIgE level was 75.3%. Overall agreement was moderate ($\kappa = 0.59$), with strong agreement for house dust mites and birch ($\kappa > 0.7$) and weak agreement for *Tyrophagus putrescentiae* and dog ($\kappa < 0.3$). When CAP was compared with SPT as the reference, the sensitivity was 75.8% and the specificity was 75.2%. Mean wheal size by SPT showed a positive correlation with sIgE levels ($r = 0.59$), which decreased with age.

Conclusion: There was a discrepancy between SPT and CAP for diagnosing allergic sensitization among inhalant allergens. The allergic sensitization and correlation between the tests decreased with age. Cautious interpretation of the clinical relevance of allergen sensitization based on SPT and CAP results is required, especially in older patients.

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Introduction

The allergic response to allergen exposure is associated with immunoglobulin E (IgE)-mediated mast cell activation and atopic sensitization and has been identified as a risk factor for allergic diseases.^{1,2} Skin prick tests (SPTs) and measurements of serum specific IgE (sIgE) antibodies are the most commonly used diagnostic tools for confirming sensitization.

Skin prick tests (in vivo) and sIgE levels (in vitro) are different tests of a biologically diverse phenomenon. SPT reaction reflects allergen-sIgE bound to the mast cell in the skin, whereas sIgE immunoassays detect the level of allergen-sIgE in serum. The SPT has been widely used to detect allergen-sIgE; it is simple and safe but uncomfortable and time consuming. Skin reactivity can be influenced by some medications, the skin tester's skill, reagents, and allergen extracts.^{3–5}

The radioallergosorbent test (RAST), the multiple allergen simultaneous test, and the CAP system are among the in vitro techniques used to detect serum sIgE with high speed and high

binding capacity. CAP is widely accepted as a standard sIgE measurement because of its reliability, reproducibility, and good agreement with SPT results.^{6–8} However, the sensitivity of CAP varies among inhalant allergens,^{9,10} and discordance between SPT and CAP results has been reported.^{8,10–13} Comparative studies of these tests have focused on only some allergens or small populations.^{8,11–16} In this study, we compared SPT with sIgE measured by CAP for various common inhalant allergens.

Methods

Study Design and Subjects

The present study was conducted retrospectively. A total of 2,635 subjects who underwent SPT at Dong-A University Hospital (Busan, Korea) from June 2011 to May 2016 were included. Serum sIgE was determined based on the subject's clinical history and SPT results and was measured using a CAP system (Phadia AB, Uppsala, Sweden). The study was approved by the institutional review board of Dong-A University Hospital.

Allergen-Specific Tests

Skin prick testing was performed with 24 common inhalant allergens including tree pollens (tree mix, birch, alder, beech, oak,

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Japanese cedar), grass pollens (grass mix, rye, timothy, orchard, Bermuda grass), weed pollens (ragweed, mugwort, Japanese hops), molds (*Alternaria* species, *Aspergillus fumigatus*, *Cladosporium* species, *Candida albicans*), and indoor allergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat, dog, *Tyrophagus putrescentiae*, cockroach). Japanese cedar extract was obtained from Lofarma (Milan, Italy) and *Alternaria* species, cat, and dog extracts were obtained from Bencard (Breford, United Kingdom); all other allergen extracts were obtained from Allergopharma (Reinbeck, Germany). Normal saline and histamine (1 mg/mL) were used as negative and positive controls, respectively. A positive SPT reaction was considered a wheal larger than 3 mm (wheal size) or a histamine reaction (allergen/histamine ratio [A/H] ≥ 1) with surrounding erythema appearing 15 minutes after exposure. Total serum IgE and sIgE levels for 17 allergens were measured using CAP, and an sIgE level of at least 0.35 kU/L was considered a positive reaction. The Phadia CAP system is an assay for sIgE characterized by a new solid phase (hydrophilic polymer encased in a capsule) combined with a secondary enzyme-linked antibody that recognizes allergen-bound patient IgE and a fluoroenzymometric detection system. Assays were performed according to the manufacturer's standard protocol (Phadia AB). Atopy status was defined as positive based on SPT reaction or sIgE level.

Statistical Analysis

Quantitative and qualitative results were expressed as mean $\pm$ SD and absolute numbers or frequencies, respectively. Descriptive statistics were performed using SPSS 12.0 (SPSS Inc, Chicago, Illinois). Statistical significance was assessed using the t test or Mann-Whitney U test for continuous variables and the Fisher exact test for categorical variables. *P* values less than .05 were considered statistically significant.

The SPT results were analyzed by wheal size and A/H. The ratio of positive results and agreement were compared using the κ coefficient between SPT and sIgE for each allergen. Sensitivity and specificity were calculated for CAP compared with SPT as the reference. Sensitivity was calculated as the number of positive CAP results among subjects with a positive SPT reaction, and specificity was calculated as the number of negative CAP results among subjects with a negative SPT reaction. The correlation between SPT wheal size and sIgE levels was calculated with the Spearman coefficient and adjusted for sex, age, and total IgE levels.

Results

Demographics

Of 2,635 patients, 1,389 were female (52%). Ages ranged from 10 to 90 years (mean age 44.4 years). Of the 2,635 patients, 2,487 (94.4%) were older than 18 years. Six hundred ninety-nine (26.5%) had bronchial asthma, 925 (35.1%) had allergic rhinitis, and 35 (1.3%) had atopic dermatitis (Table 1).

Allergen Sensitization

The proportion of positive SPT reactions to sIgE levels is presented in Table 2. The overall percentage of positive SPT responses by wheal size or by A/H was 59.8%, which was higher for wheal size (58.6%) than for A/H (47.5%). Sensitization rate for most allergens decreased with age (Fig 1).

Patients with positive SPT responses were predominantly male (53.9% vs 37.5%), younger (40.1 ± 16.6 vs 50.7 ± 16.3 years), and with higher serum total IgE levels (388.6 ± 648.1 vs 178.1 ± 534.0 kU/L) compared with those without positive responses, with a significant difference ($P < .001$ for all comparisons; data not shown).

Table 1

Clinical Characteristics of Study Subjects (N = 2,635)^a

Female	1,389 (52)
Age (y)	44.4 $\pm$ 17.3 (10–90)
Total IgE (kU/L)	306.6 $\pm$ 614.8
Disease	
BA	699 (26.5)
AR	925 (35.1)
BA with AR	288 (10.9)
Atopic dermatitis	35 (1.3)
Chronic urticaria	68 (2.6)
Food allergy	57 (2.2)
Drug allergy	58 (2.2)
Others	1,134 (43)

Abbreviations: AR, allergic rhinitis; BA, bronchial asthma; IgE, immunoglobulin E.

^aValues are presented as mean $\pm$ SD (range) or number (percentage).

Sensitization rate was the highest to *D farinae*, followed by *D pteronyssinus*. Agreement between wheal size and A/H was 98.5% for rye, 98.3% for orchard and Bermuda grass, 98.2% for Japanese cedar and *Alternaria* species, and 98% for timothy grass. Agreement was greater than 90% for all allergens, except *T putrescentiae* (85.4%).

Overall, the positive sIgE response was 52% (876 of 1,685). *Tyrophagus putrescentiae* showed the highest sensitization rate, followed by birch.

Comparison of CAP With SPT

Agreement between the SPT and sIgE level was moderate (75.8% for wheal size and 74.7% for A/H; $\kappa = 0.46$) for 17 allergens (Table 3). *Dermatophagoides pteronyssinus* and birch showed strong agreement ($\kappa > 0.7$), whereas *T putrescentiae* and dog showed weak agreement ($\kappa < 0.3$).

The sensitivity of CAP was higher compared with A/H (78.8%) and SPT wheal size (72.8%). Birch showed the highest sensitivity, followed by *D pteronyssinus* and *D farinae*. The specificity of CAP was higher compared with SPT wheal size (78.2%) and A/H (72.2%). *Dermatophagoides pteronyssinus*, Japanese hops, and mugwort showed the highest specificity (Table 4).

The SPT mean wheal size and sIgE levels were significantly correlated for all 17 allergens, except *T putrescentiae*. Birch, beech, mugwort, *D pteronyssinus*, and *D farinae* were strongly correlated ($r > 0.7$); and after adjustment for sex, age, and serum total IgE levels, beech, oak, and rye showed a strong correlation (Table 5). The correlation was compared in subjects older than 18 years for 12 allergens including birch, beech, oak, Japanese cedar, rye, Bermuda grass, ragweed, mugwort, Japanese hops, *A fumigatus*, *D pteronyssinus*, and *D farinae*. A weaker correlation was observed for older patients (>60 years) than for younger patients, except Japanese cedar, Bermuda grass, and mugwort (Fig 2).

Discussion

The diagnosis of allergy is based on the positive correlation between clinical history of symptoms on exposure to allergens and positive in vivo and/or in vitro allergy test reactions to clinically relevant allergens. In this study, we compared SPT results with sIgE levels for various common inhalant allergens.

A positive SPT reaction includes a mean wheal diameter of at least 3 mm or a ratio of at least 1 for mean wheal diameter to histamine level. The corresponding results of the 2 criteria for positive SPT responses were compared. SPT reaction was more frequently positive for wheal size (58.6%) than for A/H (47.5%). However, the overall agreement between the 2 results was very high (95.9%). For all subjects, allergic diseases including bronchial asthma, allergic rhinitis, allergic conjunctivitis, and atopic

Table 2
Positive Rate of Skin Prick Test and CAP System^a

Allergen	Total (N = 2,635)		Agreement		CAP
	Mean wheal ≥ 3 mm	A/H ≥ 1	Positive	Negative	
Tree mix	383 (14.5)	319 (12.1)	312 (11.8)	2,245 (85.2)	
Birch	326 (12.4)	282 (10.7)	275 (10.4)	2,302 (87.4)	190/350 (54.3)
Alder	337 (12.8)	279 (10.6)	275 (10.4)	2,294 (87.1)	
Beech	283 (10.7)	212 (8)	204 (7.7)	2,344 (89)	169/338 (50)
Oak	286 (10.9)	189 (7.2)	183 (6.9)	2,343 (88.9)	55/107 (51.4)
Japanese cedar	87 (3.3)	48 (1.8)	44 (1.7)	2,544 (96.5)	37/100 (37)
Grass mix	130 (4.9)	87 (3.3)	80 (3)	2,498 (94.8)	
Rye	83 (3.1)	55 (2.1)	49 (1.9)	2,546 (96.6)	44/111 (39.6)
Timothy	131 (5)	86 (3.3)	83 (3.1)	2,501 (94.9)	
Orchard	119 (4.5)	80 (3)	77 (2.9)	2,513 (95.4)	
Bermuda grass	82 (3.1)	43 (1.6)	40 (1.5)	2,550 (96.8)	34/86 (39.5)
Ragweed	127 (4.8)	79 (3)	75 (2.8)	2,504 (95)	66/188 (35.1)
Mugwort	251 (9.5)	187 (7.1)	184 (7)	2,381 (90.4)	109/235 (46.4)
Japanese hops	156 (5.9)	96 (3.6)	92 (3.5)	2,475 (93.9)	41/108 (38)
<i>Alternaria</i> sp	74 (2.8)	31 (1.2)	29 (1.1)	2,559 (97.1)	14/37 (37.8)
<i>Aspergillus fumigatus</i>	103 (3.9)	45 (1.7)	36 (1.4)	2,523 (95.7)	25/92 (27.2)
<i>Cladosporium</i> sp	91 (3.5)	36 (1.4)	31 (1.2)	2,539 (96.4)	
<i>Candida albicans</i>	181 (6.9)	89 (3.4)	76 (2.9)	2,441 (92.6)	
<i>Dermatophagoides pteronyssinus</i>	963 (36.5)	795 (30.2)	775 (29.4)	1,652 (62.7)	647/1,635 (39.6)
<i>Dermatophagoides farinae</i>	1,043 (39.6)	840 (31.9)	819 (31.1)	1,571 (59.6)	751/1,597 (47)
Cat	388 (14.7)	267 (10.1)	252 (9.6)	2,232 (84.7)	81/151 (53.6)
Dog	297 (11.3)	127 (4.8)	111 (4.2)	2,322 (88.1)	70/137 (51.1)
Cockroach	357 (13.5)	158 (6)	137 (9.1)	2,257 (85.7)	20/50 (44)
<i>Tyrophagus putrescentiae</i>	587 (22.3)	278 (10.6)	240 (9.1)	2,010 (76.3)	17/27 (63)

Abbreviation: A/H, allergen/histamine ratio.

^aValues are presented as number (percentage).

dermatitis amounted to 1,345 (51%), and atopy was present in 71.5% by SPT (70% for wheal size and 62.1% for A/H).

Skin reactivity by SPT decreased with age.¹⁷ Mean wheal sizes decreased significantly to a plateau in patients older than 60 years.¹⁷ The incidence and severity of atopic diseases reportedly decrease with age, particularly in those at least 60 years old.^{16,18} In this study, the rate of positive responses decreased with age, with the highest sensitization rate in patients 20 to 29 years old, which

was similar for various inhalant allergens. Mean wheal sizes also decreased with age and a more rapid decrease was observed in patients older than 50 years.

The in vitro measurement of sIgE is an important complementary tool to diagnose allergy. The RAST, a noncompetitive, heterogeneous (separation step included), and solid-phase immunoradiometric assay, was the first assay to be introduced for the detection for sIgE. The allergosorbent is prepared by covalently coupling an allergen of

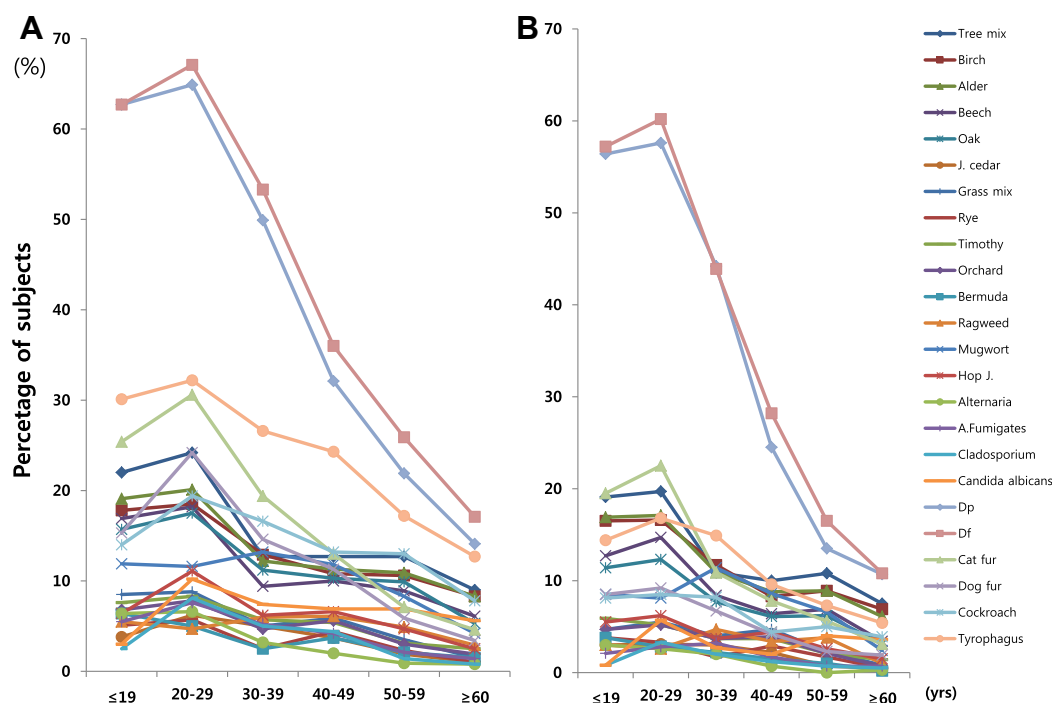


Figure 1. Sensitization rate of skin prick test to inhalant allergens in all age groups by (A) wheal size and (B) allergen/histamine ratio. A.fumigatus, *Aspergillus fumigatus*; Df, *Dermatophagoides farinae*; Dp, *Dermatophagoides pteronyssinus*; Hop J., Japanese hops; J. cedar, Japanese cedar; Tyrophagus, *Tyrophagus putrescentiae*.

Table 3

Agreement, Sensitivity, and Specificity of CAP System Compared With Skin Prick Test as the Reference

Allergen (n)	Mean wheal ≥ 3 mm				A/H ≥ 1					
	Agreement, %			κ	P value	Agreement, %			κ	P value
	Positive	Negative	Total			Positive	Negative	Total		
Birch (350)	44.9	42	86.9	0.738	<.001	40.6	44.3	84.9	0.701	<.001
Beech (338)	36.7	44.1	80.8	0.615	<.001	31.1	46.7	77.8	0.556	<.001
Oak (107)	38.3	36.4	74.7	0.495	<.001	29	43	72	0.444	<.001
Japanese cedar (100)	20	54	74	0.416	<.001	15	57	72	0.341	.010
Rye (111)	24.3	53.2	77.5	0.512	<.001	19.8	55.9	75.7	0.456	<.001
Bermuda grass (86)	24.4	54.7	79.1	0.544	<.001	11.6	55.8	67.4	0.242	.008
Ragweed (188)	23.9	56.9	80.8	0.571	<.001	18.6	61.2	79.8	0.516	<.001
Mugwort (235)	39.6	43.8	83.4	0.668	<.001	35.7	46.8	82.5	0.647	.010
Japanese hops (108)	31.5	44.4	75.9	0.516	<.001	29.6	55.6	85.2	0.682	<.001
<i>Alternaria</i> sp (37)	27	43.2	70.2	0.393	.015	18.9	56.8	75.7	0.444	.005
<i>Aspergillus fumigatus</i> (92)	10.9	63	73.9	0.287	<.005	10.9	66.3	77.2	0.35	<.001
<i>Dermatophagoides pteronyssinus</i> (1,635)	33.4	55.9	89.3	0.775	<.001	29.7	58.2	87.9	0.739	.010
<i>Dermatophagoides farinae</i> (1,597)	36.4	47.5	83.9	0.675	<.001	31.4	50	81.4	0.621	<.001
Cat dander (151)	47	22.5	69.5	0.372	<.001	39.7	31.1	70.8	0.413	<.001
Dog hair (137)	37.2	24.8	62	0.237	.005	26.3	37.2	63.5	0.274	.001
Cockroach (50)	40	24	64	0.316	.008	26	42	68	0.344	.015
<i>Tyrophagus putrescentiae</i> (27)	48.1	14.8	62.9	0.172	.365	25.9	22.2	48.1	0.01	.952
Mean	33.2	42.7	75.8	0.49		25.9	48.8	74.7	0.46	

Abbreviation: A/H, allergen/histamine ratio.

particular specificity to a cyanogen bromide-activated cellulose (paper) disk. CAP shows 3-fold higher binding capacity than RAST and decreases the nonspecific binding properties of allergosorbents using a solid.¹⁹ CAP has higher sensitivity, specificity, and efficiency than RAST.^{20–22}

Skin prick testing and sIgE differ in biological and clinical relevance, and their results are not interchangeable.¹⁹ SPTs are reportedly more sensitive but less specific than sIgE tests to diagnose allergy in patients with asthma or rhinitis.²³ However, disagreement between the SPT and sIgE has been reported.^{8,12,13,24} Overall agreement between SPT and CAP was 80.6% for 53 inhalant allergens in patients with chronic rhinitis.⁸ Variable agreement among individual allergens has been reported (ie, >85% for molds, 80%–85% for grasses, and wide variation in agreement among tree pollens, with 80%–90% specificity and 50%–80% sensitivity for CAP). A study of young children showed substantial disagreement between SPT and sIgE for 16 common inhalant and food allergens, with poor to moderate agreement ($\kappa \leq 0.6$ for all comparisons).¹² Moreover, adults with severe asthma sensitized to fungi showed

77% concordance and 23% discordance between test results. Smits et al²⁵ reported that only 43 of 100 patients (43%) undergoing SPT and CAP responded to the 2 tests. These findings suggested the need to perform the 2 tests to obtain a definitive diagnosis because of the different responses to skin and in vitro testing methods.

Most previous studies have used wheal size in SPT analyses.^{8,26–29} In this study, we defined a positive SPT reaction based on wheal size or A/H and subsequently compared SPT and CAP results. Based on wheal size, overall agreement for the 17 inhalant allergens was 75.8%, with 78.8% sensitivity and 78.2% specificity. According to A/H, the agreement was similar (74.7%), with higher sensitivity (78.8%) and lower specificity (72.2%) compared with results based on wheal size. Mean wheal size by SPT showed a positive correlation with sIgE levels for all 17 allergens tested (overall correlation $r = 0.59$). SPT reactivity decreases with age¹⁷ and differs by sex.¹⁵ In addition, high total IgE levels show more positive CAP results⁸; therefore, we adjusted for sex, age, and serum total IgE levels. Our results indicated an overall correlation of 0.45 and a positive correlation between the 2 tests, except for cockroach. One study

Table 4

Sensitivity and Specificity of CAP System Compared With Skin Prick Test as the Reference

Allergen	Mean wheal ≥ 3 mm		A/H ≥ 1	
	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %
Birch	92.4	81.7	96.6	76.4
Beech	86.1	76.8	90.5	71.2
Oak	75.9	73.6	83.8	65.7
Japanese cedar	69	76.1	71.4	72.2
Rye	77.1	77.6	81.5	73.8
Bermuda grass	80.8	78.3	71.4	66.7
Ragweed	75	83.6	83.3	78.8
Mugwort	80.2	86.6	84	81.5
Japanese hops	64.2	87.3	82.1	87
<i>Alternaria</i> sp	58.8	80	77.8	75
<i>Aspergillus fumigatus</i>	52.6	79.5	62.5	80.3
<i>Dermatophagoides pteronyssinus</i>	88.1	90	93.1	85.5
<i>Dermatophagoides farinae</i>	87	81.7	91.4	76.2
Cat dander	66.4	77.3	72.3	69.1
Dog hair	60.7	64.2	69.2	60
Cockroach	55.6	85.7	65	70
<i>Tyrophagus putrescentiae</i>	68.4	50	63.6	37.5
Mean	72.8	78.2	78.8	72.2

Abbreviation: A/H, allergen/histamine ratio.

Table 5

Correlation Between Mean Wheal Size of Skin Prick Test and Serum Specific Immunoglobulin E Levels Measured by CAP System

Allergen	Correlation (r)	P value	Correlation (r) ^a	P value
Birch	0.739	<.001	0.533	.061
Beech	0.705	<.001	0.835	<.001
Oak	0.62	<.001	0.917	<.001
Japanese cedar	0.451	<.001	0.262	.387
Rye	0.583	<.001	0.782	.002
Bermuda grass	0.635	<.001	0.431	<.001
Ragweed	0.628	<.001	0.402	<.001
Mugwort	0.724	<.001	0.385	<.001
Japanese hops	0.672	<.001	0.376	<.001
<i>Alternaria</i> sp	0.48	.003	0.45	.005
<i>Aspergillus fumigatus</i>	0.378	<.001	0.575	<.001
<i>Dermatophagoides pteronyssinus</i>	0.793	<.001	0.427	<.001
<i>Dermatophagoides farinae</i>	0.79	<.001	0.476	<.001
Cat dander	0.494	<.001	0.039	.709
Dog hair	0.466	<.001	0.367	<.001
Cockroach	0.508	<.001	−0.224	.534
<i>Tyrophagus putrescentiae</i>	0.327	.096	0.565	.088

^aPartial correlation coefficient adjusted by sex, age, and total immunoglobulin E levels.

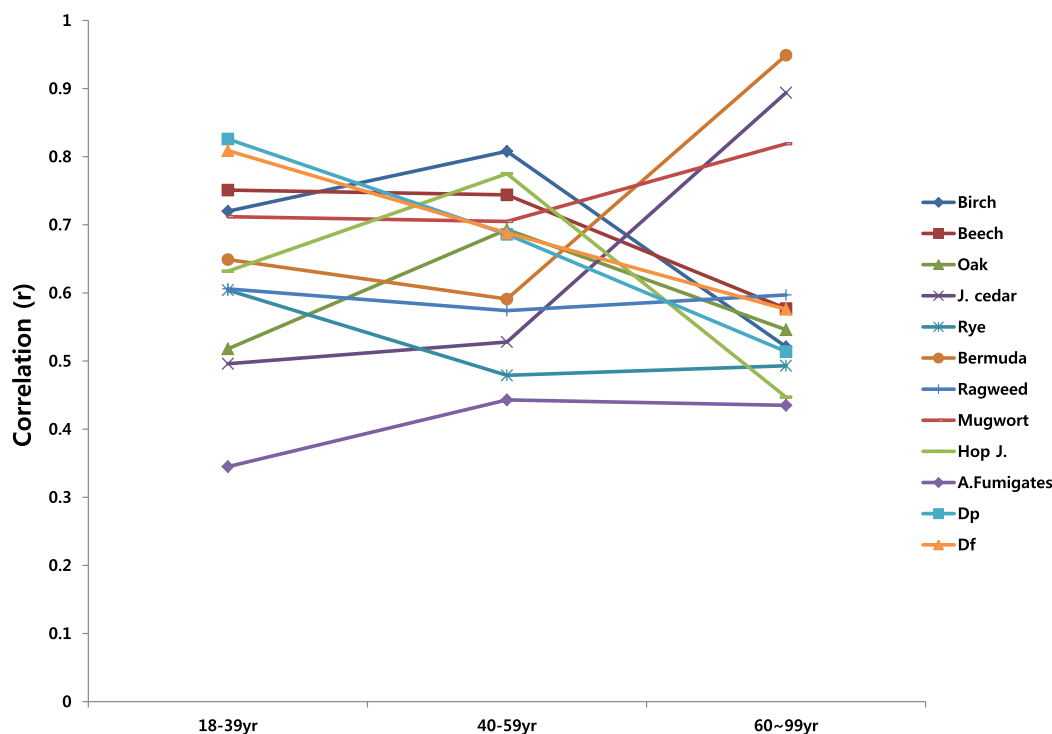


Figure 2. Correlation between mean wheal size by skin prick test and serum specific immunoglobulin E levels in all age groups. A.fumigatus, *Aspergillus fumigatus*; Df, *Dermatophagoides farinae*; Dp, *Dermatophagoides pteronyssinus*; Hop J., Japanese hops; J. cedar, Japanese cedar; Tyrophagus, *Tyrophagus putrescentiae*.

indicated that the rate of sensitization decreased with age,³⁰ which was consistent with our findings. The correlation also showed a tendency to decrease with age, especially for patients older than 60 years.

There was substantial disagreement between SPT and CAP results in this study, and the agreement, sensitivity, specificity, and correlation between the 2 tests were very wide among allergens. Environmental factors such as diet, obesity, smoking, and pets, test methodology, different allergen extracts, and population with a wide age range could contribute to the difference.

Our study had some limitations. CAP was not performed in all patients and data analysis on some allergens was inadequate. However, the study had a large sample and wide age range for subjects and included various common inhalant allergens.

There was a discrepancy between results from SPT and CAP for diagnosing allergic sensitization among inhalant allergens. Allergic sensitization and correlation between the tests decreased with age. Thus, it might be necessary to use SPT and CAP to identify allergic sensitization, especially in older patients.

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