

## ORIGINAL ARTICLE

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# Intradermal Skin Testing in Allergic Rhinitis and Asthma with Negative Skin Prick Tests

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## ABSTRACT

Taking medical history, physical examination, and performing some in vivo and in vitro tests are necessary for the diagnosis of allergy. Skin prick test (SPT) is considered as the standard method and first-line approach for the detection of allergic sensitization. Although mainly SPT is used for the detection of allergic sensitization, intradermal skin test (IDST) may be necessary, especially in patients with a negative SPT result. IDST is quite safe; however, is nowadays seldom used for detection of inhalant allergy and its value remains controversial. We aimed to investigate whether IDST is useful and necessary in diagnosis of respiratory allergies or not.

This study involved 4223 patients with allergic rhinitis (AR) and/or bronchial asthma (BA). SPT results were positive in 2419 patients (57%) and negative in 1804 (43%). IDST was applied to 344 patients with marked allergic symptoms and with negative SPT results.

Out of 344 patients, 152 (44%) showed allergic sensitization to IDST. The most commonly encountered allergic response was against the house dust mite (HDM) (32.6%). Allergic response against fungal spores was also relatively high (22%), while the pollen allergy rate (4.3%) was quite low. In BA patients with negative prick test, IDST made a significant contribution to the diagnosis of HDM allergy ( $p=0.003$ ).

To avoid missed diagnosis of AR and BA, particularly regarding the HDM allergy, application of IDST may be beneficial; therefore, IDST should be considered as the next step after SPT for diagnosis of allergy prior to in vitro or provocation tests.

**Keywords:** Aeroallergen; Allergic; Asthma; Fungal; Intradermal; Mite; Pollen; Prick; Rhinitis; Skin test

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## INTRODUCTION

Allergic rhinitis (AR) and bronchial asthma (BA) are important public health problems, affecting millions

of people worldwide. Recent studies have revealed an increasing prevalence of AR and BA worldwide.<sup>1</sup> Missed diagnosis and treatment of AR and BA may cause serious problems; therefore, more attention should be paid on the rapid diagnosis and appropriate therapy.

Currently, there are several available *in vivo* allergy tests, such as skin prick test (SPT), intradermal (also referred to as "intracutaneous") skin test (IDST), and provocation test. In individuals, who come to the hospital with signs and symptoms of allergy, the first test used to confirm allergy is the SPT.<sup>2-7</sup> However, negative SPT results do not mean that the patient does not have any allergic reactions. Physicians often encounter allergic individuals with negative SPT results. In such circumstances, IDST should be considered as a next step for the diagnosis of allergy prior to *in vitro* or *provocation* tests. SPT is preferred for its high sensitivity, simplicity, low cost, and rapid availability of results. IDST has also similar advantages.

On the other hand, in cases where skin tests cannot be done including; dermatographism, generalized dermatitis, ongoing treatment with antihistamines or tricyclic antidepressants, and any history of systemic reaction concerning the skin test and avoidance of patients from skin testing, allergic sensitivity should be determined by measuring serum specific IgE levels or other *in vitro* tests when indicated.<sup>4,7</sup>

The present study aimed to determine whether IDST is reliable and necessary in the diagnosis of AR and BA in patients with negative SPT results before the other expensive, hard or time-consuming tests, such as serum specific IgE and provocation tests.

## MATERIALS AND METHODS

This study involved 4223 patients with AR and/or BA, aged 18 to 70 years. Patients were admitted to the Department of Pulmonary Diseases, Faculty of Medicine, Balikesir University, Turkey, between January 2011 and December 2014.

Firstly, patients were tested with SPT with a panel (Allergopharma, Reinbek, Germany) containing the 19 most common regional environmental aeroallergens (50 000 BU/mL) according to the international guidelines.<sup>8,9</sup> Aeroallergens were supplied by Allergopharma Laboratorium (Allergopharma, Reinbek, Germany). The prick test included grass and cereal mix (velvet grass, orchard grass, rye grass,

timothy grass, Kentucky blue grass, meadow, and fescue, barley, oat, rye, wheat), tree I (early spring bloomers: alder, hazel, poplar, elm, willow), tree II (mid spring bloomers: birch, beech, oak, plane), weed mix (mugwort, nettle, wall pellitory, dandelion, English plantain), *Quercus robur*, *Pinus sylvestris*, *Olea europaea*, *Populus alba*, *Salix caprae*, *Dermatophagoides pteronyssinus* (DP), *Dermatophagoides farinae* (DF), dog epithelia, cat epithelia, cockroach, *Alternaria tenuis*, *Aspergillus fumigatus*, *Cladosporium herbarum*, and *Penicillium notatum*. Histamine and saline solutions were used as positive and negative controls, respectively.

SPT results were positive in 2419 patients (57%) and negative in 1804 (43%). A total of 344 patients (95 men and 252 women) with negative SPT result (among 1804 patients) had reported allergic symptoms; therefore, IDST was applied to them.

IDST was performed by injecting 0.02 mL of antigens into the outer surface of the right upper arm with a 27-gauge hypodermic needle. All skin tests were applied by the same individual and 12 standardized commercial aeroallergens (500 BU/mL) were used (Allergopharma extracts; Allergopharma, Reinbek, Germany): 4 pollens (grass mix, weed mix, tree I, tree II), 4 mites (DP, DF, *Tyrophagus putrescentiae*, *Lepidoglyphus destructor*) and 4 mould spores (*Alternaria tenuis*, *Aspergillus fumigatus*, *Cladosporium herbarum*, *Penicillium notatum*). The negative and positive controls consisted of diluent solution (phenol-saline solution) and histamine (0.17 mg/mL histamine dihydrochloride) (Allergopharma), respectively. The reactions were evaluated 15 min after injection, and both wheal and erythema diameters measured; 3 mm above the negative control was considered as a positive test result.<sup>2-4</sup> We asked participants to avoid use of first generation antihistamines for at least 3 days, and to avoid using long-acting antihistamines and phenothiazine derivatives of tricyclic antidepressants for at least 7 days before testing.

Statistical analyses were performed using SPSS 21 (IBM Corp, NY, USA). The data were compared using chi-square or Fisher's exact test, depending on whether there was a difference between groups. A p value of less than 0.05 was considered statistically significant.

The local ethics committee of Balikesir University approved the study protocol and it was registered as clinical trial (No. 2015/05).

**RESULTS**

As seen in Table 1, we applied IDST for pollen allergens in 282 patients, house dust mites in 344 patients, and fungal spore in 323 patients. Data obtained applying IDST to patients with negative SPT results indicated that 152 out of 344 individuals (44%) showed allergic sensitivity. We also observed significant correlation between symptoms and IDST results in all patients.

The total number of intradermally applied antigens was 3173, of which 250 tests were confirmed as positive (7.9%).

The frequency of mite allergy was higher than that of fungal spores and pollen allergies (mite 32.6%, fungal spore 22%, pollen 4.3%) (Table 1).

Test positivity was examined one-by-one, and the highest positivities were found in DP, aspergillus, and

DF (26.2%, 17.2%, and 16.6%, respectively).

In terms of sex, it was deduced that women were more prone to house dust mite allergy (DP, DF) than men ( $p < 0.05$ ). The rate of house dust mite allergy sensitivity for women was 39%, while it was about 29% for men.

The average age of patients was 40.96 (range, 18–70). To evaluate whether there is any difference between allergic sensitivity and age of the individuals, the individuals were divided into two groups (below and above 45 years of age). However, no statistically significant difference ( $p > 0.05$ ) between two groups was observed.

In BA patients with negative prick test, IDST provided additional benefits in the diagnosis of house dust mite allergy, which was also identified as statistically significant ( $p = 0.003$ ) (Table 2).

**Table 1. Number of allergic rhinitis and asthma patients tested and percentage of positive cases for antigenic sensitivity**

Antigens		Number of patient applied	Number of positive cases	Percentage of positive cases (%)
Pollens	TOTAL	282	12	4.3
	Grass mix	282	5	1.8
	Weed mix	282	6	2.1
	Tree I (Early spring bloomers)	282	5	1.8
	Tree II (Mid spring bloomers)	282	0	0.0
Mites	TOTAL	344	112	32.6
	Dermatophagoides pteronyssinus	344	90	26.2
	Dermatophagoides farinae	344	57	16.6
	Tyrophagus putrescentiate	155	11	7.0
	Acarus siro	140	6	4.0
Fungal Spores	TOTAL	323	71	22
	Alternaria tenius	302	6	1.9
	Aspergillus fumigatus	269	48	17.2
	Cladosporium herbarum	224	7	3.1
	Penicilium notatum	267	10	3.7

**Table 2. Intradermal skin test positivity with respect to allergic rhinitis and asthma**

Topics	AR	AR+BA (1)	BA (2)	TOTAL BA 1+2	TOTAL
All patients	207	97	40	137	344
Allergic patients *	84	53	15	68	152
Pollens	9	3	0	3	12
Mites	54	46	12	**58	112
Fungal Spores	41	14	16	30	71

AR: Allergic Rhinitis ,BA: Bronchial Asthma

\*Multiple allergic sensitivities were observed in some patients.

\*\*  $p=0.003$

No adverse effects were observed during or after the use of IDST.

## DISCUSSION

SPT is a skin testing most widely used for evaluating inhalant allergy being considered the standard test for diagnosis of respiratory allergy.<sup>2-7</sup> IDST is another type of skin testing, which must be the second step in allergy testing. IDST is also more sensitive than the SPT and can usually provide more consistent results. These skin tests are preferred for their high sensitivity, easy application, low cost, allowing the evaluation of multiple allergens at one session, and the rapid availability of results. IDST is also minimally invasive and, when applied correctly, has good reproducibility.

While IDST remain an essential part of the diagnostic workup for hymenoptera allergy,<sup>7</sup> usefulness of IDST with aeroallergens in the diagnosis of AR and BA is still controversial.<sup>8-14</sup> Based on the negative or positive false results in the studies on IDST, some researchers including Openheimer et al,<sup>10</sup> Nelson et al,<sup>11</sup> Wood et al<sup>12</sup> and Schwindt et al<sup>13</sup> recommended abstaining from using IDST in the diagnosis of allergy, while some others, like Larrabee et al,<sup>14</sup> Peltier et al,<sup>15</sup> and McKay et al<sup>16</sup> encourage physicians to use IDST when SPT results are negative in patients showing symptoms and signs of allergy. Likewise, Larrabee<sup>14</sup> and McKay et al<sup>16</sup> found that DP and DF were the most likely antigens to demonstrate a positive intradermal response after a negative SPT.

Similar to the findings of Larrabee<sup>12</sup> and McKay et al,<sup>14</sup> in this study, it was shown that use of IDST for detection of house dust mites sensitivity in AR and BA patients with negative SPT results is very beneficial. Otherwise, some of the patients in this study (about 44%) would remain undiagnosed in spite of the distinctive symptoms of AR and BA.

Previous studies showed that skin test reactivity to aeroallergens in the general population increases through childhood, peaks in young adulthood, and decreases after the age of 50 years.<sup>2,4</sup> In the present study; however, concerning allergic sensitivity and the age of the individuals, there was no statistically significant difference ( $p>0.05$ ). In light of this finding, we recommend taking the patient's clinical history into consideration to perform IDST in adults regardless of age.

On the other hand, Calabria et al<sup>17</sup> and Cohn et al<sup>18</sup> reported that IDST result has a high negative predictive value, i.e. a negative IDST result may be helpful for ruling out inhalant allergic sensitivity.

In a mega study (20 530 patients, 878 583 wheals), Gordon et al reported that 80 systemic reactions occurred following IDST.<sup>19</sup> They found the risk of overall systemic reaction rate about 0.009% with no hospitalization and no fatalities.

Our findings are compatible with the above-mentioned study; we applied totally 3173 IDST to 344 individuals without any remarkable side effect. Therefore, IDST is also quite safe and applicable for patients showing allergic signs with negative SPT results.

Consequently, IDST is a useful and reliable method for the diagnosis of respiratory allergies in negative SPT patients. This study has shown that IDST is required in AR and BA, under certain conditions. Particularly, IDST should not be ignored for the SPT negative patients with anamnesis indicating house dust mite allergy and should be applied as next step after SPT, prior to other tests.

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Fuat Erel conceived, designed and did data collection and manuscript writing, did review and final approval of manuscript.

Nurhan Sarioglu, Mehmet Kose, and Mucahide Gokcen collected the study data and wrote the manuscript. Mustafa Kaymakci, Ahmet Hamdi Kepekci did the review. Mehmet Arslan did the statistical analysis.

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