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ORIGINAL ARTICLE

Comparison between Specific Immunoglobulin E and Skin Prick Test for Diagnosis of Allergic Patients

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ABSTRACT

Background: *Skin prick test (SPT) has been identified as the gold standard method to diagnose IgE mediated hypersensitivities; it is accurate, easy and cheap. However, SPT has some important limitations, so in vitro serum specific serum IgE (sSIgE) detection can be a good alternative. The diagnostic yield of sSIgE testing usually depends on the specific allergen.* ***Objective:*** *This study compares between SPT and sSIgE for diagnosis of allergy.* ***Methodology:*** *61 allergic patients enrolled from Zagazig University Allergy and Immunology Unit, tested by SPT for the common allergens. Serum total IgE and specific IgE levels were measured and compared to SPT results.* ***Results:*** *The over- all sensitivities of sSIgE were excellent (75-100%) for most of allergens tested. PPV was excellent with some allergens (pollens, cockroaches, mites) and poor with others (cat hair). Sensitivity of mites sSIgE was excellent with PPV approaching 90%, specificiy was only 13%. However, the NPV was 100%. Significant level of agreement and correlation between the results of SPT and sSIgE for cockroaches and molds was reported. Positive correlation between the total levels of serum IgE and the diameter of wheal and flare of the SPT for mites, pollens and cockroaches was found.* ***Conclusion:*** *The sensitivities of sSIgE were excellent for most of allergens tested. Specificity of sSIgE varies between individual allergens. Serum specific IgE testing may be a good alternative to skin prick test if the latter could not be carried out.*

INTRODUCTION

The prevalence of allergic diseases is rapidly increasing and affects 30–40% of population worldwide[1]. In 2025, about 400 million of individuals will be at risk of allergic asthma and 500 million would suffer from allergic rhinitis[2].

Atopic march is a characteristic pathway of allergy; the condition usually starts with papular urticaria and food allergies during childhood, followed by respiratory allergy; allergic asthma and allergic rhinitis later on[1].

Although genetic factors had long been appreciated to a major effect on development of allergic diseases, environmental factors are equally important in the expression of this genetic potential. So, air pollution, allergen exposure, smoking, lifestyle changes, early life infections, hygiene hypothesis[3], diet, psychological stress all are influencing the sensitization of allergen and prevalence of allergy[4,5].

In allergic patients there is continuous production of allergen-specific IgE. This condition is defined as sensitization[6]. Atopic infants usually suffer from sensitization to one single allergen (mono-sensitization), then, sensitization to other allergens develops[7].

The diagnosis of allergic diseases is based on the integration between a typical history of allergic symptoms and diagnostic tests. In vivo (skin tests) and in vitro tests used in the diagnosis of allergic diseases, they are directed towards the detection of free or cell-bound IgE[8].

Diagnosis of allergy can be carried out by different methods. This includes testing for the presence of allergens, for the presence of allergen-specific IgE in serum, for IgE-mediated response, and by provocation with allergen[9].

Many technical developmental steps had occurred in the field of skin tests since their innovation in 1865 by Blackley; intra-dermal testing, skin prick testing[10], standardization, and further validation[11]. Skin testing is very sensitive, simple, accurate, safe and less expensive test that measures the results of histamine release from mast cells in the skin, and provides a relevant "on-the-spot" result for the patient[12].

However, in some circumstances, the performance and interpretation of skin tests are conflicting: the patient is on antihistamines therapy[13]; infant patients could not withstand skin testing; seasonal variation[14]; possible severe reactions in risky patients; or the condition of the skin, i.e., due to dermographic urticaria or other skin pathologies. Skin tests should never be performed unless a physician and emergency equipment are available immediately to treat systemic reactions. Quality, stability and concentration of allergenic extracts are important points to be strictly controlled. All these are limiting factors of skin testing for diagnosis of allergy[15,16]

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Detection of specific serum IgE (sSIgE), although generally less sensitive than skin testing, is an appropriate alternative with some specific advantages: testing is not influenced by antihistamines; many allergens can be assayed with a limited amount of serum, which can be stored for subsequent testing; and testing is, apart from the need to draw blood, not invasive. It should be mentioned that these types of assays only provide information about the presence of allergen-specific IgE (sensitization), but not about the clinical status of the patient[17].

The objective of this study is to determine the accuracy of specific serum IgE measurement compared to skin prick test as the gold standard for examining allergen sensitization of individual to several allergens

METHODOLOGY

Study design and Subjects

This cross sectional study was carried out during the period from Feburary - December 2019. Inclusion criteria were: allergic patients referred to Allergy and Immunology Unit, Zagazig University Hospitals, with ages between 6 and 59 years, free from other chronic diseases and signed informed consent, and had stopped antihistamincs and corticosteroids for 7 days. The exclusion criteria included pregnancy or breast feeding, patients with skin pathology, malignancy, autoimmunity, hypertensive patients on beta blockers therapy. Approval of the ethical committee was obtained from Faculty of Medicine, Zagazig University 6444/2019.

Skin testing:

This was done and interpreted by the allergist using home-made allergen extracts from the following allergens: Mites (*Dermatophagoides pterossinus* and *Dermatophagoides farina*), date palm pollens, house dust, cockroaches, cat hair, pigeon feather, molds, wool and cotton. This was performed on the volar aspect of the forearm skin after proper disinfection, one drop of each allergen extract was applied to the skin, at least 2 cm apart. After pricking the skin, excess allergen was wiped off. Histamine was used as a positive control and 50% glycerol saline solution was used as a negative control. After 15 minutes, the forearm skin was examined, erythema and induration were measured with a ruler and recorded. Wheals twofold larger in diameter than the histamine control or showing a pseudopod were classified as 4+. If the wheal was 3 mm or up to two times larger than the histamine control, it was classified as 3+. If it was more than one-half the size of the positive control it was scored as 2+; if it was more than one-quarter of the size of the positive control it was scored as 1+; and if it was less than one-quarter of the size of the positive control it was scored as 0. Scores of 2+ or more were defined as positive[18].

Blood sampling and serum collection

Five milliliters of whole blood were collected for immunoassay. After centrifugation, serum was aliquoted and frozen at -20°C for storage until processing.

Total and specific serum IgE testing

Serum samples were tested for total IgE and specific IgE levels. Total IgE was measured by ELISA according to manufacture instruction (Chemus Bioscience, USA).

Specific IgE levels were estimated using AllergyScreen®, a quantitative in vitro system that determines the presence of allergen-specific IgE antibodies in human serum. Different allergens are bound to the surface of a nitrocellulose membrane, 250 µl of patient seum were pipetted into the reaction trough and allowed for incubation at room temprature for 45 minutes. The allergen-specific IgE antibodies in patient seum will bind to the specific allergens on the membrane. Washing was done to remove the non-bound IgE antibodies .

Detector polyclonal anti-human IgE antibody was added and incubated at room temperature for another 45 minutes. These biotin labelled detector antibodies identified the allergen-specific IgE from the patient serum.Washing step removed the non-bound detector antibodies .

The membrane was then incubated with a streptavidin-conjugate at room temprature for 20 minutes. The streptavidin conjugate binds to the biotin of the detector antibody. Washing removes the non-bound streptavidin-conjugate. The substrate was added to the membrane and allowed for incubation at room temperature for 20 minutes, a blue band was developed on the respective allergen line. The reaction was stopped by washing. After drying the membrane thoroughly, the colouration of the allergen lines was evaluated by Improvio scanners.

The concentration of specific IgE in the serum sample was determined, specific IgE level < 0.35 kU/L was considered negative and ≥ 0.35 kU/L was considered positive. The results were graded into classes: 0 (under 0.35 kU/L), 1 (0.35–0.7 kU/L), 2 (0.7–3.5 kU/L), 3 (3.5–17.5 kU/L), 4 (17.5–50 kU/L), 5 (50–100 kU/L), and 6 (100 kU/L).

The specificity and sensitivity of the specific IgE were calculated. Sensitivity, indicats the true positive rate and specificity represents the true negative rate. Correlations between results of SPT and total and specific IgE levels were calculated by Spearman correlation and kappa agreement test, p value of less than 0.05 was considered significant. Statestical tests were performed using SPSS software.

RESULTS

This study included 61 participants; 19 males and 42 females. The mean age of study participants was 23 years (6-59). 31% of participants were males and 69 % were females. The mean level of total IgE was 631 IU/ml. Respiratory allergies and skin allergies were detected in 67% and 44 % of patients respectively (some patients showed both allergies). Allergic rhinitis was diagnosed in (34%) of patients followed by asthma (33%), atopic dermatitis (31%) and chronic urticaria (13%). (table 1)

Table 1: Demographic and clinical criteria of the study population

Total No	61	No	%
Age(mean)	23 year (6-59 range)		
Sex	Female Male	42 19	69 31
Clinical Diagnosis	**Respiratory allergies**	**41**	**67**
	Allergic rhinitis/ rhino-conjunctivitis	21	34
	Bronchial asthma	20	33
	Skin allergies	**27**	**44**
	Atopic dermatitis	19	31
	Chronic urticaria	8	13
Total IgE (mean)	631 IU/ml		

Sensitization to date palm pollens and house dust mites were the most sensitization detected via SPT, followed by cat hair, cockroaches. Regarding sSIgE results, mite sensitization was the most prevalent, followed by pollens, cat hair, cockroaches and molds. Agreement between the results of SPT and sSIgE was variable among allergens. The level of agreement for cockroaches and molds sensitization was perfect (kappa 0.9 and 0.7, respectively). Slight agreement was found for other allergens. Measurement of sSIgE against house dust, wool and cotton was not applicable. House dust and wool sensitizations were detected in 74% and 33% of subjects that underwent SPT respectively . (table 2)

Table 2: Prevalence of positive tests among the study population:

Allergen	**SPT n (%)**	**sSIgE n (%)**	**Kappa (Agreement)**
Mites	53 (87%)	60 (98%)	0.2
Date palm pollens	56 (92%)	42 (69%)	0.3
House dust	45 (74%)	NA	-
Cockroaches	21 (34%)	23 (38%)	0.9
Cat hair	22 (36%)	39 (64%)	0.1
Pigeon feather	21 (34%)	12 (20%)2	0.6
Molds	15 (25%)	21 (34%)	0.7
Wool	20 (33%)	NA	-
Cotton	2 (3%)	NA	-

Kappa <0: No agreement, (0.00-0.20): slight agreement, (0.21-0.40): fair agreement, (0.41 - 0.60): moderate agreement,(0.61-0.80): substantial agreement, (0.81 - 1.00): almost perfect agreement." NA: not applicable.

Sensitivity and specificity of sSIgE were compared to SPT as the gold standard test for each allergen. The over- all sensitivities of sSIgE were excellent (75-100%) for most of allergens tested. However, sensitivity for pigeon feather was somewhat less than other allergens. PPV was excellent with some allergens and poor with others (cat hair).

Specificity of sSIgE varies between individual allergens, the specificity of sSIgE against mites was the least (13%), specificity of tests against pollens, pigeon feather and cockroaches were excellent with NPV (26-100%) (table 3)

Table 3: sensitivity and specificity of sSIgE compared to SPT

	Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
Mites	100%	13%	88%	100%	89%
Date palm pollens	75%	100%	100%	26%	77%
Cockroaches	100%	95%	91%	100%	97%
Cat hair	100%	62%	59%	100%	75%
Pigeon feather	57%	100%	100%	81%	85%
Molds	100%	87%	71%	100%	90%

PPV: positive predictive value, NPV: negative predictive value

Significant correlation between the diameter of wheal and flare of SPT and sSIgE result in all the tested allergens was detected. Good correlation (r = 0.51 to 0.75) was observed for pollens, cockroaches, molds and pigeon feather, however a fair correlation (r = 0.26 to 0.50) were shown for mites and cat hair.

Positive correlation between the total levels of serum IgE and the diameter of wheal and flare of the SPT for mites, pollens and cockroaches. The bigger the diameter of the wheal and flare of SPT, the higher the levels of serum IgE observed, this was not the case with cat hair, pigeon feather and molds allergens (table 4).

Table 4: Correlation between SPT and sSIgE and total IgE results for different allergens:

SPT	sSIgE		Total IgE	
	R	P value	r	*P* value
Mites	0.3	0.009	0.4	0.00 *
Date palm pollens	0.8	0.0	0.8	0.00*
Cockroaches	0.7	0.0	0.6	0.00*
Cat hair	0.4	0.0006	0.06	0.6
Pigeon feather	0.6	0.0	0.04	0.7
Molds	0.7	0.0	0.1	0.3

r : correlation coefficient ,
P value < 0.05 indicates significance.

DISCUSSION

Skin prick and serum specific IgE testing are both designed to detect immediate hypersensitivity reactions. SPT has been the most popular testing method especially in patients with history and physical findings suggesting allergic disease. However, the history is sometimes complex and many allergens may be involved. Also, SPT has some important limitations. In vitro sIgE detection can be a good alternative[19]. However, the diagnostic yield of SPT and sSIgE testing can differ, depending on the specific allergen[20]. Serum specific IgE testing has many advantages; It is easy, painless, as serum is obtained, it can be tested for IgE of differenet allergens, or subjected to other immunologic investigations, and results of different studies can be easily compared. This provides greater consistency and standardization[21].

In this study, the majority of the patients were female (69%). This finding was observed in most previous studies in Italian[22],Asian[23,25,25], and American[18] subjects, and in Egptian studies as well[26,27]. It was postulated that girls with early menarche , have twice the risk of developing allergy after puberty compared with those in whom menarche occurs later[28]. The cyclical variations in sex hormone levels with the menstrual cycle may also influence allergic symptoms. This may indicate the role of estrogen in triggering mast cell degranulation, moreover, mast cell is known for expressing α-estrogen receptor[29].

In the current research, respiratory allergies (allergic rhinitis and bronchial ashma) were the most diagnosed clinical conditions, this comes in accordance with Alimuddin et al.[25], (63.8%) of their study population were presented with history of asthma and allergic rhinitis. Other studies had reported that allergic rhinitis was diagnosed in 75- 96% of patients tested[18.23].

Pollens and house dust mites had the highest prevalence of positive results in SPT among all tested allergens. This is usually due to the warm and humid climate of Sharkia Governorate. Specific IgE against house dust mites was detected in 92% of cases. A study conducted on 182 mite allegic patients had observed that mite specific IgE was detected in all subjects[30]. This is to great extent similar to data recorded by previous studies in Thailand and Malaysia[23,24]. This differs from other investigators which reported that 20% of mite-allergic people did not have IgE to either of mite allergens[31,32]. The discrepancies may be due to variation in the geographic location and the used methodology.

This study revealed significant levels of agreement and correlation between the results of SPT and sSIgE for cockroaches and molds, which is similar to results obtained by Visitsunthorn et al[23] and Cho et al.[33]Good correlation was shown for mucor in a study conducted by Asha'ari and colleuges[24]. However, slight agreement and correlation were detected for house dust mites and cat hair in the present study , this comes in accordance with Asha'ari findings[24]. On the other hand Visitsunthorn and collegues[23] had reported good agreement between cat hair sIgE and mean wheal diameter of SPT and low level of agreement for house dust mites. Another study observed high agreement and correlation for cat hair and mites[33].

Findings of this study indicate good correlation between the total levels of serum IgE and the diameter of wheal and flare of the SPT for mites, pollens and cockroaches which was not found for cat hair, pigeon feather and molds allergens. This finding is partially similar to those of Asha'ari study that had reported positive correlation for mites and molds[24]. A Sweden study showed that correlation between SPT and total IgE levels varies between different allergens[34]. Genetics, environmental factors and study population may contribute to the differences between studies.

In the current study, the over- all sensitivities of sSIgE were excellent (75-100%) for most of allergens tested. PPV was excellent with some allergens (pollens, cockroaches, mites) and poor with others (cat hair). Sensitivity of mite sSIgE was excellent with PPV

approaching 90%, specificiy was only 13%, however, the NPV was 100%. These findings are quite similar to those obtained by Asha'ari et al.[24], where sensitivity of serum specific IgE testing for house dust mites was 86%, and specificity was 45.5%. A Group of Indonisian researches had been studing the accuracy of specific serum IgE measurement compared to skin prick test for mites, they found that PPV of serum specific IgE testing was excellent (>90), however the NPV was low[25]. Lower sensitivitiy (75%) and higher specificty (90%) were detected by Calabria et al.[35] Another study reported high sensitivity and specificity of serum specific IgE testing for Der p and Der f allergens [(85%, 93.3%) and (87.5%, 89.6%)][36]. Several studies had postulated that dust mites sSIgE levels have been shown to be highly predictive of clinical allergy, even at very low levels[37,38].

This study revealed that seum specific IgE for cockroaches had high sensitiviy and specificity, with excellent PPV and NPV. These findings agree with those of an Indian study that reported high sensivity of cockroaches (92.8%), with specificity of 66.6%, PPV of 86%, and NPV of 80%[39]. Alimuddin and colleauges[25] reported that sensitivity, specificity, PPV and NPV of sSIgE for cockroach were 23.8% 98.3% 90.9% 64.4% respectively. However another study showed low sensitivity of cockroach specific IgE testing (34.5%) and high specificity (88.2%) [35].

Potential cross-reactions between different allergenic extracts should be considered when interpreting the results of both skin tests and in vitro tests. There are shared allergens (e.g., tropomyosin) between mites and cockroaches that may coexist in populations that are exposed to both allergens resulting in cross-reactivity. Assessments of allergen exposure in patient environment can help to judge whether positive IgE responses are due cosensitization or due to allergenic cross-reactivity[40].

We noted that although sSIgE for cat hair had high sensitivity and low specificity,it showed low PPV and excellent NPV. These findings come in agreement with those of Asha'ari et al.[24], where sensitivity, specificity, PPV and NPV for cat hair were 90%, 45%, 33% and 94% respectively.

CONCLUSION

The sensitivities of sSIgE were excellent for most of allergens tested. Specificity of sSIgE varies between individual allergens. Serum specific IgE testing may be a good alternative to skin prick test if the latter could not be carried out.

Limitations: Relatively small number of study population.

Conflicts of interest:
The authors declare that they have no financial or non financial conflicts of interest related to the work done in the manuscript.

- Each author listed in the manuscript had seen and approved the submission of this version of the manuscript and takes full responsibility for it.
- This article had not been published anywhere and is not currently under consideration by another journal or a publisher.

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