Original Article

Total serum immunoglobulin E level and specific allergens in adults with skin diseases

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Abstract

Background: Immunoglobulin E (IgE) plays an important role in allergic diseases. Although several studies have shown the association of serum total IgE and allergen-specific IgE levels with allergic dermatological diseases such as atopic dermatitis, there are few studies addressing this association for skin diseases in general.

Aims: We sought to evaluate IgE levels in skin diseases and investigate the differences based on the disease type and clinical factors such as gender and age.

Methods: Data from 2836 patients who visited the dermatologic clinic of the Konkuk University Hospital, Seoul, Republic of Korea for 4 years were reviewed to document IgE levels and clinical information. IgE levels were collated with the type of skin disease, gender, and age.

Results: Patients with atopic dermatitis had a much higher total IgE level and were more susceptible to allergens as compared to other disease groups. Patients in other disease groups showed no significant differences in IgE levels. Men showed higher total IgE levels but the gender differences decreased with increasing age.

Limitations: The data were collected from patients at a referral centre and thus may not represent the general population of dermatologic patients. There was a lack of information regarding factors that could potentially influence IgE levels such as smoking history and disease severity.

Conclusions: The results suggest that there are physiological or environmental differences in IgE-mediated immune responses between males and females. Also, except for atopic dermatitis, there were no clinical differences in the IgE levels among various skin diseases.

Key words: Atopic dermatitis, immunoglobulin E, multiple allergens simultaneous test, skin diseases

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Introduction

Immunoglobulin E (IgE) plays an important role in allergic reactions.[1] It is the least abundant Ig isotype and accounts for only 0.05% of the total Ig concentration.[2] In atopic individuals, however, IgE levels may be increased by over 1000 times.[3] IgE levels to specific allergens may be associated with the occurrence or aggravation of some diseases.[4,5]

The skin prick test has been used to evaluate an individual's sensitivity to specific allergens. However, this test cannot be performed in patients with severe skin manifestations or in patients on anti-allergy medications. Also, false negative results may occur in individuals with low skin reactivity, such as in very young or old patients, and false positive results may be seen in patients with hyperactive skin, such as in patients with dermographism.[6,7] The multiple allergens simultaneous test (MAST) is less invasive and uses the patient's serum. It shows high sensitivity and specificity[8] and since it does not have the limitations of the skin prick test it has been more widely adopted in clinical practice.

The role of IgE in dermatologic diseases has been mostly studied in allergic diseases such as atopic dermatitis (AD), allergic contact dermatitis, and urticaria.[9-12] Although IgE levels have been studied in other skin diseases such as herpes zoster and alopecia areata,[13,14] there are few studies addressing a broader category of skin diseases.

The aim of this study was to evaluate the total and allergen-specific IgE levels in skin diseases in general and to analyze the differences

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according to the disease type. In addition, we sought to investigate the correlation of IgE levels with sex and age.

Methods

Study population

The records of patients who visited the dermatologic clinic of the Konkuk University Hospital, Seoul, Republic of Korea between July 2011 and June 2015 were screened. The following patient data were collected retrospectively: total serum IgE level, MAST results, age, sex, and diagnosis. Because the level of total serum IgE is higher in children than those in adults,[15,16] analyses were restricted to adult patients aged 21–80 years. This study was conducted in accordance with the Declaration of Helsinki and Korean Good Clinical Practice, and approval from the institutional review board was obtained.

Total serum immunoglobulin E

Total serum IgE levels were measured by a fluorescent enzyme immunoassay using the ImmunoCAP™ 250 system (Pharmacia Diagnostics, Uppsala, Sweden). The detectable range of total serum IgE level was 2–5000 kU/L. Measurements less than 2 kU/L or greater than 5000 kU/L were expressed as 2 kU/L or 5000 kU/L, respectively.

Allergen-specific immunoglobulin E

Allergen-specific IgE was assessed using MAST with the AdvanSure™ AlloScreen kit (LG Life Sciences, Seoul, Korea), which is also based on an enzyme immunoassay. The results were divided into seven classes according to the levels of IgE (class 0–6); results of class 2 or more were considered significant positives.

We collected data for specific allergens, which were divided into shared or common allergens, inhalant panel-specific allergens, and food panel-specific allergens.

Statistical analysis

The data distribution for total serum IgE levels was highly skewed and leptokurtic. Therefore, to achieve a Gaussian distribution, natural logarithmic transformation of the IgE level was applied prior to statistical analysis. The Student's *t*-test and one-way analysis of variance were used for comparing the mean IgE levels. Chi-square test was used to compare categorical data, and correlations were evaluated by Pearson correlation analysis. The Cochrane Armitage trend test was used to analyze the trend of MAST positivity according to age. Bonferroni correction was performed for multiple comparisons. *P* values less than 0.05 were considered statistically significant. All statistical analyses were performed using the SPSS software (SPSS for Windows, Version 17.0, SPSS Inc., Chicago, IL, USA).

Results

Clinical data

Gender and age

Table 1 shows the demographic information of all patients. There were 811 males and 1452 females, with no significant gender differences among the age groups ($P = 0.18$). The mean age of all patients was 40.8 years, and the mean age was not significantly different in males and females ($P = 0.111$).

Diagnostic groups

A total of 65 diagnoses were documented, which were categorized according to Fitzpatick's Dermatology in General Medicine[17] and Korean Textbook of Dermatology[18] into the following 11 diagnostic groups: AD, urticaria, dermatitis excluding AD, pruritus, infectious skin diseases, drug eruption, erythematous diseases, papulosquamous diseases, diseases of the skin appendages, cutaneous vascular diseases, and miscellaneous diseases.

Among the above diagnostic groups, the last six groups each constituted less than 68 (3%) patients were reclassified into a single "other diseases" category in order to achieve clarity and conciseness in the analysis. Thus, seven diagnostic groups were compared: AD, urticaria, dermatitis excluding AD, pruritus, infectious skin diseases, drug eruption, and other diseases. Table 2 shows the sex ratio and mean age of the patients in each diagnostic group. The proportion of males in the AD group was higher than that in the other diagnostic groups ($P = 0.022$). There were no significant differences in the sex ratio among the other diagnostic groups ($P = 0.096$). The mean age of patients with AD was significantly lower ($P < 0.001$) than that of the other groups.

Total serum immunoglobulin E level

Gender and age

The mean serum IgE level of all patients was 99 kU/L, and males had significantly higher IgE levels as compared to females

Table 1: Demographic data of patients with geometric mean of total serum immunoglobulin E level, and multiple allergens simultaneous test-positivity rate according to gender and age

Demographic characteristics	*n* (%)	Mean age (SD), years	Male sex, *n* (%)	Geometric mean of total serum IgE (95% CI), kU/L	Percentage of ≥1 specific allergen, *n* (%)
Total	2263 (100)	40.8 (14.5)		99 (93-104)	1029 (45.5)
Gender					
Male	811 (35.8)	41.5 (14.9)		154 (139-169)*	445 (54.9)*
Female	1452 (64.2)	40.4 (14.3)		77 (72-83)	584 (40.2)
Age (years)					
21-30	742 (32.8)		247 (33.3)	111 (100-123)	404 (54.5)†
31-40	499 (22.1)		184 (36.9)	92 (81-104)	237 (47.5)
41-50	387 (17.1)		141 (36.4)	95 (82-109)	161 (41.6)
51-60	378 (16.7)		130 (34.4)	93 (80-107)	147 (38.9)
61-70	185 (8.2)		79 (42.7)	94 (77-114)	57 (30.8)
71-80	72 (3.2)		30 (41.7)	94 (64-138)	23 (31.9)

*Significantly higher than females ($P<0.001$), †MAST-positivity rate significantly decreased with increasing age (Cochrane Armitage trend test, $P<0.001$).
SD: Standard deviation, CI: Confidence interval, MAST: Multiple allergens simultaneous test, IgE: Immunoglobulin E

($P < 0.001$, Table 1). Patients aged 21–30 years showed a slightly higher serum IgE level (111 kU/L) than other age groups, although the difference was not statistically significant ($P = 0.159$). We compared sex differences in IgE levels according to age groups, and found that elderly patients (61–80 years) showed a less prominent difference between genders than patients aged 21–60 years [Figure 1].

Diagnostic groups

Table 2 and Figure 2 show the mean IgE values of each diagnostic group. Patients with AD had a higher mean IgE level (401 kU/L), which was over four times higher than that of all the other diagnostic groups combined (93 kU/L). The urticaria group also showed a significantly higher IgE level than the other groups. There were no other significant differences among the remaining diagnostic groups. Overall, 110 (4.9%) patients had extremely high levels of total serum IgE (above 1000 kU/L). Thirty-three of these patients were diagnosed with AD constituting 34.7% of the AD group, while the remaining 77 were distributed evenly among the other diagnostic groups (3.6% of the non-AD groups).

Allergen-specific immunoglobulin E

Gender and age

MAST positivity was significantly higher in males [$P < 0.001$, Table 1]. The number of patients who had five or more positive allergens and who had a sum of classes of ten or more were also higher in males [Table 3]. The MAST positivity rate significantly decreased with increasing age [$P < 0.001$, Table 1].

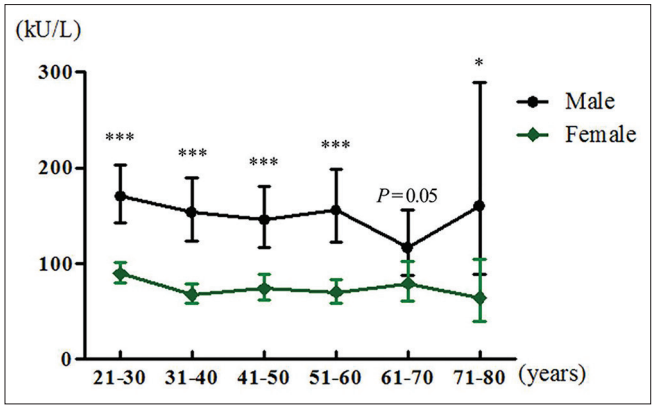

Figure 1: Gender differences of the geometric mean and 95% confidence interval of total serum immunoglobulin E level according to age groups. *$P = 0.018$, ***$P < 0.001$

Diagnostic groups

Table 2 shows the MAST-positivity rates among the diagnostic groups. The AD group showed a significantly higher rate of MAST positivity (78.9%, $P < 0.001$, which was lower than the adjusted significance threshold level of 0.0024 after Bonferroni correction). None of the other groups showed significant differences in MAST-positivity rates ($P = 0.017$, which was higher than the adjusted significance threshold level of 0.003). In addition, patients with AD had more positive allergens and a higher value of the sum of classes than all the non-AD patients combined [$P < 0.001$, Table 3].

Frequent allergens

The most common allergens overall were *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, and house dust regardless of sex, age, or diagnosis. In the inhalant panel, Russian thistle, sweet vernal grass, and reed were the most frequent allergens. Bermuda grass, goldenrod, dandelion, and sallow willow were also frequent in some subgroups. Young patients, especially those between 21 and 30 years of age, and AD patients were most strongly sensitized to *Penicillium chrysogenum*, a fungus producing the antibiotic penicillin. In the food panel, flour mite (*Acarus siro*), garlic, and onion were the most common allergens. In addition, the fungus *Candida albicans*, beef, pork, peanut, and wheat flour were frequently detected in the food panel.

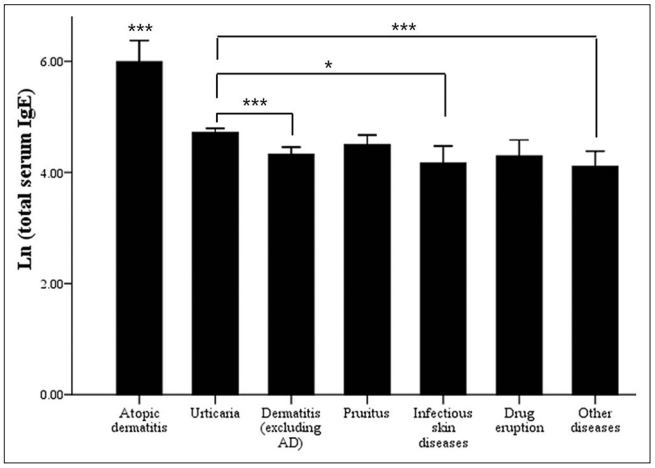

Figure 2: Mean of the natural logarithm of total serum immunoglobulin E levels among diagnostic groups. *$P < 0.05$, ***$P < 0.001$, P values were corrected for multiple comparisons

Table 2: Number, sex ratio, age, geometric mean of total serum immunoglobulin E level, and multiple allergens simultaneous test-positivity rate according to diagnostic group

Diagnostic group	*n* (%)	Male sex, *n* (%)	Mean age (SD), years	Geometric mean of total serum IgE (95% CI), kU/L	Percentage of ≥1 specific allergen, *n* (%)
Atopic dermatitis	95 (4.2)	45 (47.4)	28.6 (7.8)	401 (274-586)	75 (78.9)
Urticaria	1103 (48.7)	140 (37.2)	38.9 (13.4)	112 (104-121)	526 (47.7)
Dermatitis (excluding atopic dermatitis)	515 (22.8)	185 (35.9)	42.5 (14.6)	76 (67-86)	211 (41)
Pruritus	257 (11.4)	90 (35)	48.2 (15.4)	90 (76-107)	99 (38.5)
Infectious skin diseases	80 (3.5)	22 (27.5)	41.9 (13.4)	65 (48-88)	35 (43.8)
Drug eruption	86 (3.8)	23 (26.7)	45.2 (15.5)	74 (55-98)	31 (36)
Other diseases	127 (5.6)	36 (35.8)	40.3 (15.4)	61 (46-80)	52 (40.9)

SD: Standard deviation, CI: Confidence interval, IgE: Immunoglobulin E

Table 3: Differences of the number of positive allergens and the sum of classes of positive allergens according to sex and atopic dermatitis status

At least one positive allergen (*n*=1029)	Sex		Atopic dermatitis or not	
	Males (*n*=445)	Females (*n*=584)	Atopic dermatitis (*n*=75)	Nonatopic dermatitis (*n*=954)
≥5 positive allergens (%)	32.1*	18.7	48*	22.6
≥10 sum of classes of positive allergens (%)	53.9*	38.7	69.3*	43.4

*Significantly higher than females or patients with nonatopic dermatitis (P<0.001)

Correlations between total serum immunoglobulin E level and clinical indices

We analyzed the correlation of total serum IgE level with other clinical indices such as age, MAST positivity, number of positive allergens, and sum of classes of positive allergens. MAST-positive patients had significantly higher IgE levels than MAST-negative patients. The geometric mean (95% confidence interval) was 50 (47–54) kU/L for the MAST-negative group and 220 (204–237) kU/L for the MAST-positive group ($P < 0.001$). The number of positive allergens and the sum of classes were positively correlated with IgE, and the latter had a higher correlation coefficient [Table 4]. The IgE levels were not correlated with the age of the patient ($P = 0.068$).

Discussion

In general, the concentration of serum IgE increases from birth until the age of 15 years, and then decreases during adulthood.[15,16] Furthermore, males tend to have a higher level of serum IgE than females.[19-22] In this study, the most prominent results were the differences between males and females, and those between AD and non-AD patients. No overall age-dependence of total serum IgE level was observed in this study. The slight increase in the IgE levels of patients aged 21–30 years could be attributed to a predominance of patients with AD in that age group (70 of 95, 73.7%). However, the sex difference in serum IgE level and hypersensitivity to a certain allergen decreased with increasing age.

The observed increase in total serum IgE in males was consistent with the results of previous studies. Although some studies found no gender differences,[23-25] most related studies have demonstrated that total IgE levels were higher in men than in women.[26] Some authors have suggested that a higher prevalence of smoking in men could explain this phenomenon;[23,27] however, Kerkhof *et al*.[20] found that the IgE level was higher in men than in women, independently of smoking status. We were unable to find any previous reports investigating the potential mechanism or pathophysiological difference at the molecular level to explain this gender difference. Johnson *et al*.[28] showed that there was no sex difference in the IgE level in cord blood, and Chen *et al*.[26] suggested that sex hormones could play a role by regulating mast cell activation and Th2 immune responses. In the present study, although we did not record the smoking history of the patients, the gender difference in the IgE level was sufficiently large to overcome any potential influence of smoking. Furthermore, men showed an increased sensitivity to specific allergens as well as a greater number and intensity of positive allergens than women. However, it is possible that sex hormones affected the serum IgE level, considering our result that the discrepancies between genders decreased in patients aged over 60, as the inequality of sex hormones between males and females decreases with age.

Among the diagnostic groups, patients with AD showed a prominently higher level of total serum IgE, a larger proportion of patients hypersensitive to specific allergens, and a higher number and sum of classes of positive allergens. These findings were similar to the results of previous studies.[5,29] Although the mean total IgE level of patients with urticaria was higher than that of some diagnostic groups, the differences were not particularly remarkable. There was no significant difference between the mean IgE level of pruritus patients and that of other diagnostic groups. Furthermore, the proportion of patients with MAST-positivity among urticaria patients was not significantly higher than that in the other diagnostic groups, and this proportion was lower in patients with pruritus. Urticaria can be caused by both immunological and nonimmunological mechanisms. In immunological urticaria, IgG plays a key role in the immune response rather than IgE.[30] In addition, many reports have shown that the high serum IgE level in nonallergic skin diseases was due to diverse immune mechanisms, including Th1 and Th2 immune responses.[13,14,31] Therefore, it could be suggested that there was no clinical difference in the total and specific IgE levels of patients with urticaria (which is usually considered an allergic disease) and those with other skin diseases, except for AD.

We investigated the frequency of each allergen in all patients as well as according to gender, age groups, and diagnostic groups. Most groups followed the same frequency order of allergens as that observed for all inidividuals; however, we found remarkable differences in the youngest age group (21–30 years) and in the AD group, in which *P. chrysogenum* ranked first. *P. chrysogenum* is a fungus producing β-lactam antibiotics, and its spores are an important human allergen;[32] indeed, 44 (74.6%) of the 59 patients with AD were found to be sensitized to *Penicillium* in a previous study,[33] suggesting that younger patients and/or those with AD may be particularly susceptible to fungi and pollens.

This study has some limitations. First, we did not record the severity of the diseases. There might be significant gender differences regarding disease severity that could affect the results. Second, the number of patients in each diagnostic group was not equal. Almost half of the patients were diagnosed with urticaria, and patients with AD accounted for only 4.2% of the sample. We also did not analyze certain diagnostic groups in detail, such as papulosquamous diseases, including psoriasis, erythematous diseases, vascular diseases, and various tumour conditions, which were grouped together in the "other diseases" category. Finally, because majority of the patients were referred from local clinics, the disease entity and measurements of IgE may not represent the condition of the general population of dermatologic patients.

Conclusion

There were diverse differences in total and specific serum IgE levels according to the diagnostic groups and the clinical factors such as gender and age. We found that men showed a higher level of total serum IgE and specific IgE than women among patients with skin

Table 4: Correlations between total serum immunoglobulin E level and clinical indices

Index	Correlation coefficient	*P*
Age	−0.038	0.068
Number of positive allergens	0.482	<0.001
Sum of classes of positive allergens	0.51	<0.001

diseases. Also, patients with AD showed a significantly higher level of total serum IgE and greater hypersensitivity to specific allergens than those with other diagnoses. Therefore, clinicians should consider these factors while interpreting the total serum IgE level and the specific allergens.

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Conflicts of interest
There are no conflicts of interest.

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