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Effects of age, Gender and Allergen Type on Immunoglobulin E Level in Asthma and Allergic Rhinitis Patients

Marwa Baker Ahmed[1], Ali Hussein Ad'hiah[2]*
[1]*Biotechnology department, College of Science, University of Baghdad, Baghdad, Iraq*
[2]*Tropical-Biological Research Unit, College of Science, University of Baghdad, Baghdad, Iraq*

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Abstract

This study aimed to determine the effects of age, gender, and allergen type on serum immunoglobulin E (IgE) levels in asthma (AS) and allergic rhinitis (AR) patients. Sixty AS patients, 52 AR patients, and 61 controls were enrolled in the study. Sera of participants were assessed for total IgE level and specific IgE antibody against four allergen types (animal dander, grasses, mites, and molds). The results revealed that median level of total IgE was significantly increased in AS (218.9 IU/mL; *p*-value < 0.001) and AR (244.3 IU/mL; *p*-value < 0.001) patients compared to controls (167.1 IU/mL), while, there was no significant difference between AS and AR patients (*p*-value = 0.270). Logistic regression analysis demonstrated that the increased level of IgE was associated with an increased risk of AS (Odds ratio = 96.93) and AR (Odds ratio = 66.37). Receiver operating characteristic (ROC) curve analysis confirmed the predictive significance of IgE in AS and AR. The estimated area under the curve (AUC) for IgE in AS was 0.889 (*p*-value < 0.001), and at a cut-off value of 183.7 IU/mL, the sensitivity and specificity were 86.7 and 83.6%, respectively. Almost similar figures were estimated in AR, but the AUC was slightly lower (AUC = 0.873). The IgE level was not influenced by age groups (< 16, 16 – 40, and > 40 years) in AS patients or controls, while, it showed a significantly decreased level in the age group > 40 years of AR patients compared to the corresponding lower age groups (196.3 *vs.* 252.2 and 264.9 IU/mL, respectively). With respect to gender, the IgE levels showed no significant differences between males and females of patients or controls. For allergen type, mites were the most encountered allergen in age groups and males and females of AS and AR patients, and there were no significant differences between age or gender groups regarding the distribution of seropositive and seronegative patients. Further, the allergen type had no significant influence on the total IgE level. In conclusion, this study indicated the predictive significance of IgE in AS and AR. This significance was not influenced by age, gender, or allergen type.

Keywords: Asthma; Allergic rhinitis; Immunoglobulin E; Age; Gender; Allergen type.

تأثيرات العمر والجنس ونوع المواد المسببة للحساسية على مستوى الغلوبولين المناعي الكلي E في مرضى الربو والتهاب الأنف التحسسي

مروة بكر أحمد[1] ، علي حسين ادحيه[2]*
[1]قسم التقنيات الاحيائية، كلية العلوم، جامعة بغداد، بغداد، العراق
[2]وحدة البحوث البيولوجية للمناطق الحارة، كلية العلوم، جامعة بغداد، بغداد، العراق

*Email: dr.ahadhiah@sc.uobaghdad.edu.iq

الخلاصة

هدفت هذه الدراسة إلى تحديد آثار العمر والجنس ونوع المواد المسببة للحساسية على مستوى الغلوبولين المناعي الكلي (IgE) E في مرضى الربو وحساسية الانف. شملت الدراسة 60 مريضا للربو و52 مريضا لحساسية الانف و61 من افراد سيطرة. تم تقييم أمصال المشاركين لمستوى IgE الكلي واضداد IgE النوعية ضد أربعة أنواع من مسببات الحساسية (وبر الحيوانات والأعشاب والعث والفطريات). أظهرت النتائج بأن المستوى المتوسط من إجمالي IgE قد زاد بشكل كبير في مرضى الربو (218.9 وحدة دولية / مل؛ قيمة الاحتمالية < 0.001) ومرضى حساسية الانف (244.3 وحدة دولية / مل؛ قيمة الاحتمالية < 0.001) مقارنة بالسيطرة (167.1 وحدة دولية / مل). بينما لم يكن هناك فرق معنوي بين مرضى الربو وحساسية الانف (قيمة الاحتمالية = 0.270). أظهر تحليل الانحدار اللوجستي أن زيادة مستوى IgE كان مرتبطًا بزيادة خطر الاصابة بالربو (الخطر النسبي = 96.93) وحساسية الانف (الخطر النسبي = 66.37). أكد تحليل منحنى خاصية تشغيل المستقبِل (ROC) الأهمية التنبؤية لـ IgE في الربو وحساسية الانف. كانت المساحة المقدرة تحت المنحنى (AUC) لـ IgE في الربو هي 0.889 (قيمة الاحتمالية < 0.001)، وبقيمة حدية قدرها 183.7 وحدة دولية / مل، كانت الحساسية والنوعية 86.7 و 83.6٪ على التوالي. وتم تقدير أرقام مماثلة تقريبًا في حساسية الانف، ولكن كانت المساحة المقدرة تحت المنحنى أقل بقليل (AUC = 0.873). لم يتأثر مستوى IgE بالفئات العمرية (<16 و 16–40 و > 40 سنة) في مرضى الربو أو مجموعة السيطرة، بينما أظهر انخفاضًا كبيرًا في المستوى في الفئة العمرية > 40 سنة لمرضى الانف التحسسي مقارنةً بالمرضى في الفئات العمرية الاقل (196.3 مقابل 252.2 و 264.9 وحدة دولية / مل على التوالي). فيما يتعلق بالجنس، لم تظهر مستويات IgE أي فروق ذات دلالة إحصائية بين الذكور والإناث من المرضى أو مجموعة التحكم. وبالنسبة لنوع المواد المسببة للحساسية ، كان العث هو أكثر مسببات الحساسية في الفئات العمرية والذكور والإناث مرضى الربو وحساسية الانف، ولم تكن هناك فروق ذات دلالة إحصائية بين الفئات العمرية أو الجنس فيما يتعلق بتوزيع المرضى الموجوبين والسالبين المصل. وفضلا عن ذلك، لم يكن لنوع المواد المسببة للحساسية أي تأثير كبير على مستوى IgE الكلي. وفي الاستنتاج، أشارت هذه الدراسة إلى الأهمية التنبؤية لـ IgE في الربو وحساسية الانف، ولم تتأثر هذه الأهمية بالعمر أو الجنس أو نوع المواد المسببة للحساسية.

1. Introduction

Asthma (AS) and allergic rhinitis (AR) are two of the most chronic inflammatory diseases of the lower and upper airways, respectively. The estimated global prevalence of AR is 10-20%, and around 300 million individuals worldwide suffer from AS [1]. AS is characterized by largely reversible obstruction of airflow, hyperresponsiveness of airways, and respiratory symptoms (wheeze, cough, shortness of breath, and chest tightness) due to inflammatory reactions that arise from interactions between host genetic components and environmental triggers (aeroallergens) [2]. A variety of innate and adaptive immune cells are involved in the pathophysiology of AS. They include innate lymphoid type 2 cells and T helper (Th) lymphocytes (Th2 and Th17), as well as regulatory and follicular helper T cells [3]. However, the hallmark features of AS airway inflammation is mediated by Th2 cells via type 2 cytokines, which include interleukin-4 (IL-4), IL-5, and IL-13, after exposure to different aeroallergens [4]. These cytokines stimulate the degranulation of mast cells, promote airway eosinophilia and leukocytosis, and enhance B-cell to produce the immunoglobulin E (IgE), and as a consequence, bronchial hyperresponsiveness (BHR) is progressed in AS patients [5]. In AR, the inflammation involves the mucosa of the upper airways, and it is also driven by Th2 cytokines with symptoms of sneezing, nasal discharge and pruritus, and obstruction of airflow in response to IgE-mediated reactions [6]. The inflammation is triggered by exposure

to aeroallergens that are recognized by antigen-specific IgE receptors present on mast cells and basophils in previously sanitized individuals [7].

Although the mechanism of AS and AR is complex, the pathophysiology and exacerbation of both allergies include the role of IgE, which has been documented to play a major role in mediating AS and AR [8], [9]. However, the serum level of IgE may be influenced by the age and gender of patients, as well as, allergen type may have an effect [10-13]. Therefore, this study sought to explore total and specific IgE in serum of Iraqi AS and AR patients, with an emphasis on age and gender.

2. Materials and methods

2.1. Populations studied

After the approval of the Ethics Committee at Al-Karkh and Al-Rusafa Health Departments (Iraqi Ministry of Health and Environment), a case control study was conducted on AS and AR patients from December 2019 – February 2020. The enrolled patients were 60 with AS (mean age ± SD = 27.5 ± 18.2 years; 27 males and 33 females) and 52 with AR (mean age ± SD = 32.4 ± 17.6 years; 20 males and 32 females). They were referred to the Allergy Specialized Centers in the Al-Karkh and Al-Rusafa administrative districts in Baghdad for diagnosis and treatment. The guidelines of the Global Initiative for Asthma (GINA) and Allergic Rhinitis and their impacts on Asthma (ARIA) were followed in the diagnosis AS and AR, respectively [14], [15]. A control sample of 61 children attending health care units (for ages < 16 years) and blood donors (mean age ± SD = 27.1 ± 14.0 years; 25 males and 36 females), who had no signs or symptoms of AS and AR or other respiratory diseases were also included in the study.

2.2. Determination of total and specific IgE

Three milliliters of peripheral blood were drawn from each patient or control subject and dispensed in a plain tube. The blood was left to clot at room temperature (20 - 25°C), and then it was centrifuged (3000 rpm at 4°C) for 10 minutes. The serum was collected, divided into aliquots and kept frozen at -20°C until assessments. The total level of IgE was determined in the obtained sera using an enzyme-linked immunosorbent assay (ELISA) kit (Euroimmun, Germany). The sera were also profiled for specific IgE against 25 inhalation allergens using a multiplex immunoblot kit (Euroimmun, Germany). It is a qualitative and quantitative test kit that detects specific IgE antibodies. The kit was supplied with blot strips pre-coated with 25 different inhalation allergens. The strips were incubated with the sera of patients in a first reaction step. If these sera contained specific IgE antibodies, they bind to the coated allergens. The bound antibodies were detected using a conjugate enzyme (enzyme-labelled anti-human IgE) that produced a color reaction. Due to a low sample size of AS and AR patients, only four main allergen types were qualitatively screened and analyzed (animal dander, grasses, mites, and molds). In both cases, the instructions of the manufacturer were followed.

2.3. Statistical analysis

The serum level of IgE was first tested for normality using Kolmogorov-Smirnov and Shapiro-Wilk tests. It was found that the level did not follow a normal distribution; therefore, it was given as a median and interquartile range (IQR: 25 – 75%). Significant differences between medians were assessed using either Mann-Whitney *U* (to compare two groups) or Kruskal–Wallis (to compare more than two groups) test. Pearson Chi-square test (χ^2) or two-tailed Fisher exact test was used to assess significant differences between categorical variables. Logistic regression analysis was used to calculate the odds ratio (OR) and 95% confidence interval (CI). Receiver operating characteristic (ROC) curve analysis was performed to estimate the area under the curve (AUC), sensitivity, and specificity of total IgE. A probability (p) value ≤ 0.05 was considered significant. The statistical package IBM SPSS version 25.0 was used to perform these analyses.

3. Results

3.1. Total IgE level

Median level of total IgE was significantly increased in AS (218.9 [IQR: 198.5-2449] IU/mL; *p*-value < 0.001) and AR (244.3 [IQR: 196.3-268.3] IU/mL; *p*-value < 0.001) patients compared to controls (167.1 [IQR: 150.3-178.1] IU/mL), while, there was no significant difference between AS and AR patients (*p*-value = 0.270) (Figure 1).

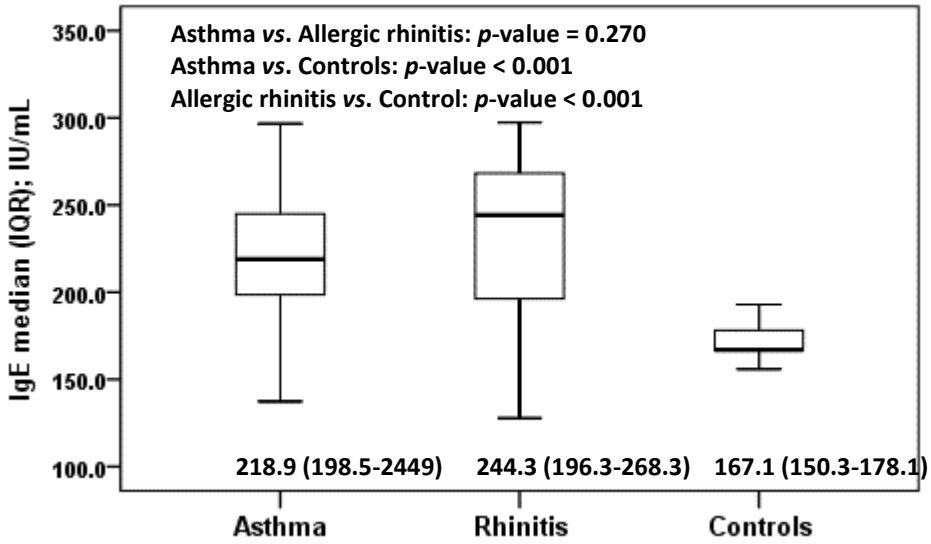

Figure 1- Serum total IgE level in patients (asthma and allergic rhinitis) and controls

According to the median level of total IgE, AS and AR patients and controls were classified as high (> Median) or low (≤ Median) group. Most AS and AR patients were classified as high median groups (76.7 and 69.2%, respectively), while only 3.3% of the controls were found in the high group. The difference in both cases was highly significant (p-value < 0.001). Logistic regression analysis revealed that the high group was associated with an increased risk of AS (OR = 96.93) and AR (OR = 66.37) (Table 1)

Table 1-Asthma and allergic rhinitis patients and controls stratified according to the median level of IgE.

Group	IgE Level; IU/mL				OR	95% CI	*p*-value
	High (> Median)		Low (≤ Median)				
	N	%	N	%			
Control (N = 61)	2	3.3	59	96.7	Reference		
Asthma (N = 60)	46	76.7	14	23.3	96.93	21.24 - 442.42	< 0.001
Allergic rhinitis (N = 51)	36	69.2	16	30.8	66.37	14.60 - 301.79	< 0.001

OR: Odds ratio; CI: Confidence interval; p: Two-tailed Fisher exact probability.

ROC curve analysis confirmed the predictive significance of total IgE in AS and AR. The estimated AUC for IgE in AS was 0.889 (95% CI: 0.819 – 0.959; p-value < 0.001), and at a cut-off value of 183.7 IU/mL, the sensitivity and specificity were 86.7% and 83.6%, respectively. Almost similar figures were estimated in AR, but the AUC was slightly lower (AUC = 0.873) (Figure 2 and Table 2).

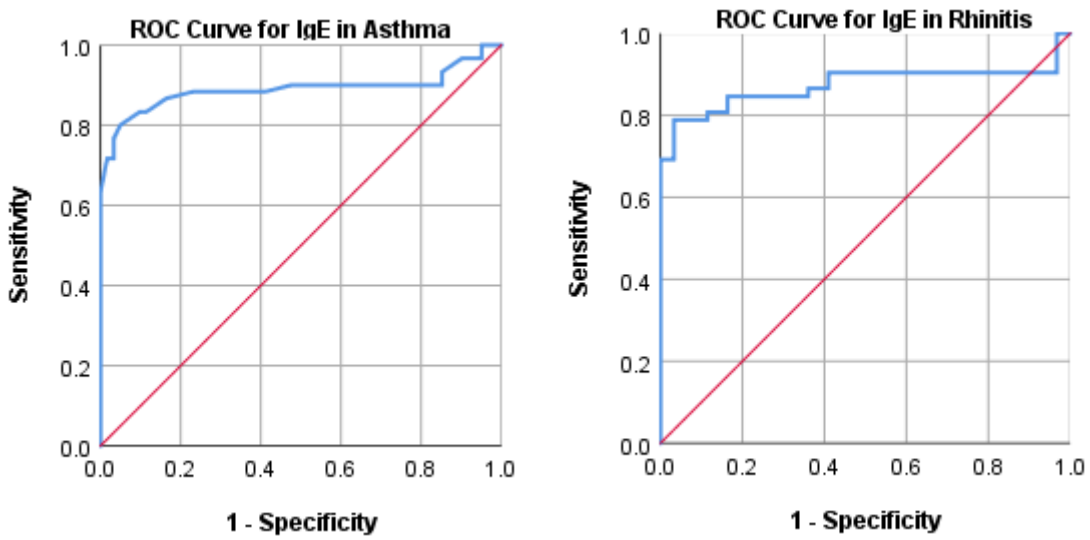

Figure 2-ROC curve analysis of total IgE in asthma and allergic rhinitis patients showing area under curve.

Table 2-ROC curve analysis of total IgE in asthma and allergic rhinitis patients.

Group	AUC	95% CI	*p*-value	Cut-off value; IU/mL	Sensitivity; %	Specificity; %
AS	0.889	0.819 – 0.959	< 0.001	183.7	86.7	83.6
AR	0.873	0.792 – 0.953	< 0.001	182.9	84.6	83.6

AS: Asthma; AR: Allergic rhinitis; AUC: Area under curve.

3.2. Total IgE level distributed according to age groups

In the three age groups (< 16, 16 – 40 and > 40 years), the total IgE levels were significantly increased in AS and AR patients compared to controls. The IgE level was not influenced by age groups in AS patients or controls, while, it showed a significantly decreased level in the age group > 40 years of AR patients compared to the corresponding lower age groups (196.3 *vs*. 252.2 and 264.9 IU/mL, respectively) (Table 3).

Table 3-Median level of IgE in sera of patients (asthma and allergic rhinitis) and controls according to age groups.

Age group; year	IgE median level (IQR: 25 – 75%); IU/mL		
	Asthma (N = 60)	Allergic rhinitis (N = 52)	Controls (N = 61)
< 16	217.1 (200.4 - 244.9)^{A}	252.2 (240.9 - 268.3)^{A}	167.1 (150.3 - 178.1)^{B}
16 – 40	218.9 (193.0 - 243.1)^{A}	264.9 (231.7 - 282.0)^{A}	168.9 (150.3 - 181.8)^{B}
> 40	224.5 (202.2 - 274.4)^{A}	196.3 (174.0 - 243.6)^{B}	167.1 (163.3 - 174.4)^{C}
p-value	0.703	0.001	0.372

IQR: Interquartile range; *p*: Kruskal-Wallis test probability. Different superscript letters denote significant differences between medians in rows, while similar letters denote no significant difference.

3.3. Total IgE level distributed according to the gender

Males and females of patients (AS and AR) showed significantly increased medians of IgE level compared to the corresponding gender groups in controls. However, the levels of IgE showed no significant differences between males and females of patients or controls (Table 4).

Table 4-Median level of IgE in sera of patients (asthma and allergic rhinitis) and controls according to gender.

Gender	IgE median level (IQR: 25 – 75%); IU/mL		
	Asthma (N = 60)	Allergic rhinitis (N = 52)	Controls (N = 61)
Male	218.9 (200.4 - 244.9)^{A}	252.2 (184.9 - 272.6)^{A}	167.0 (163.3 - 178.1)^{B}
Female	217.8 (196.7 - 244.9)^{A}	241.0 (196.3 - 264.9)^{A}	172.6 (167.0 - 183.7)^{B}
p-value	0.654	0.486	0.505

IQR: Interquartile range; *p*: Mann-Whitney *U* test probability. Different superscript letters denote significant differences between medians in rows, while similar letters denote no significant difference.

3.4. Allergen types

The sera of patients were tested for four allergen types (animal dander, grasses, mites, and molds). Mites were the most encountered allergen in age and gender groups of AS and AR patients, but there were no significant differences between age or gender groups regarding the distribution of seropositive and seronegative patients (Tables 5 and 6).

Table 5-Asthma and allergic rhinitis patients saccording to age group and allergen type.

Allergen type N (%)	Age groups; year					
	Asthma (N = 60)			Allergic rhinitis (N = 52)		
	< 16 (N = 24)	16 – 40 (N = 16)	> 40 (N = 20)	< 16 (N = 16)	16 – 40 (N = 16)	> 40 (N = 20)
Seronegative	5 (20.8)	4 (25.0)	8 (40.0)	4 (25.0)	5 (31.3)	7 (35.0)
Animal dander	3 (12.5)	0 (0.0)	1 (5.0)	1 (6.3)	2 (12.5)	0 (0.0)
Grasses	2 (8.3)	2 (12.5)	1 (5.0)	1 (6.3)	1 (6.3)	3 (15.0)
Mites	8 (33.3)	6 (37.5)	6 (30.0)	5 (31.3)	4 (25.0)	4 (20.0)
Molds	1 (4.2)	1 (6.3)	1 (5.0)	2 (12.5)	1 (6.3)	3 (15.0)
Mixed	5 (20.8)	3 (18.8)	3 (15.0)	3 (18.8)	3 (18.8)	3 (15.0)
Analysis	χ^2 = 4.913; D.F. = 10; *p*-value = 0.896			χ^2 = 6.926; D.F. = 10; *p*-value = 0.732		

Table 6-Asthma and allergic rhinitis patients according to gender and allergen type.

Allergen type N (%)	Gender			
	Asthma (N = 60)		Allergic rhinitis (N = 52)	
	Male (N = 27)	Female (N = 33)	Male (N = 20)	Female (N =32)
Seronegative	6 (22.2)	11 (33.3)	5 (25.0)	11 (34.4)
Animal dander	3 (11.1)	1 (3.0)	0 (0.0)	3 (9.4)
Grasses	1 (3.7)	4 (12.1)	1 (5.0)	4 (12.5)
Mites	8 (29.6)	12 (36.4)	6 (30.0)	7 (21.9)
Molds	2 (7.4)	1 (3.0)	3 (15.0)	3 (9.4)
Mixed	7 (25.9)	4 (12.1)	5 (25.0)	4 (12.5)
Analysis	χ^2 = 5.678; D.F. = 5; *p*-value = 0.338		χ^2 = 4.720; D.F. = 5; *p*-value = 0.450	

Stratification of patients for the four allergens revealed no significant differences between the medians of IgE between AS patients or AR patients, and the same observation was made when AS patients were compared to AR patients (Table 7).

Table 7-Median level of total IgE in sera of patients (asthma and allergic rhinitis) strartified according to allergen type.

Allergen type	IgE median level (IQR: 25 – 75%); IU/mL		p_1-value
	Asthma (N = 60)	Allergic rhinitis (N = 52)	
Seronegative	218.9 (207.8 - 259.6)	233.4 (190.6 - 258.5)	0.901
Animal dander	178.1 (155.9 - 248.5)	264.9 (245.6 - 285.0)	0.400
Grasses	278.1 (218.9 - 289.3)	196.3 (196.3 - 281.6)	0.222
Mites	222.7 (209.7 - 257.8)	254.3 (238.8 - 273.6)	0.131
Molds	218.9 (193.0 - 233.8)	231.7 (174.0 - 243.0)	0.905
Mixed	196.7 (170.7 - 230.1)	239.0 (196.3 - 264.9)	0.112
p_2-value	0.136	0.423	

IQR: Interquartile range; p_1: Mann-Whitney *U* test probability; p_2: Kruskal-Wallis test probability. Different superscript letters denote significant differences between medians in rows, while similar letters denote no significant difference.

Discussion

The data of this study demonstrated the role of IgE in the pathogenesis of AS and AR, and its levels were elevated in sera of patients compared to healthy individuals. The upregulation was associated with an elevated risk of both respiratory allergies by 96.93 and 66.37 folds, respectively, as revealed by logistic regression analysis. The biomarker diagnostic significance of IgE was also supported by ROC curve analysis, which estimated an AUC in AS and AR (0.889 and 0.873, respectively). Accordingly, the predictive significance of IgE in AS and AR was determined with sensitivity and specificity that exceeded 80%. Consistent with these findings, it has been strongly proposed that an elevated level of total IgE is a hallmark of AS and AR. Therefore, to diagnose both respiratory allergies and their severity, determining the total level of IgE in the peripheral blood can be considered a useful biomarker in pediatric and adult populations [9], [16], [17]. As presented in the introduction, the mechanism underlying the elevated level of IgE in AS and AR is complex, but it is associated with cytokines produced by activated helper T lymphocytes in response to allergens that are processed and presented by antigen-presenting cells in the airways and lungs [3], [5], [7]. The interaction of cytokines with B lymphocytes induces these cells to synthesize allergen-specific IgE that binds to a high affinity IgE receptor (FcεRI) on mast cells, which in turn these cells are activated to release histamine, cytokines, chemokines, and other mediators of AS and AR [18]. The most important cytokine is IL-4, which promotes IgE production. Thus, it is recommended to diagnose AS and AR by clinical criteria accompanied by the measurement of total and specific IgE levels [4].

When total IgE was explored in age groups of AS and AR patients (< 16, 16 – 20, and > 40 years), the level tended to show progressively elevated levels that paralleled age groups in AS patients, but the difference was not significant. In AR patients, an opposite observation was made, and the level tended to show decreased level as age was progressing. In fact the level was significantly decreased in the older age group (> 40 years) compared to < 16 and 16 – 20 age groups. In a previous study, it has been found that serum IgE level (total and specific) was significantly downregulated as a function of age in AS and AR patients, and a correlation with age was suggested [19]. Further evidence depicted that serum IgE tended to show lower levels in elderly patients with allergic diseases [20]. In a recent Iraqi study, the level of IgE was significantly decreased in the age group > 45 years of AS patients compared to patients in younger age groups, and it also tended to have a decreased level in the same age group of AR patients but the difference was not significant [13].

For gender groups, there was a tendency for males to have a higher level of IgE than females in AS or AR groups, but the differences did not attend a significant level, and the level of IgE may not be affected by gender. In two studies from Brazil and India, it has been reported that plasma levels of IgE were higher in AR males than in females, but the Brazilian study made a focus on young adults [21], [22]. In Iraqi AS patients, the total IgE level was also significantly increased in males compared to females in the age group 16 – 45 years. However, these differences were not observed in AR patients [13]. In American patients with chronic rhinosinusitis, conflicting results were found and females were presented with elevated IgE levels compared to males [23].

In the case of specific IgE antibody, around 30% of AS and AR patients were seronegative for the tested allergens, and around 70% of patients were seropositive, with mites accounting for 33.3 and 25.0% of AS and AR cases, respectively. However, there were no significant age- or gender-associated variations in these frequencies. Almost comparable frequencies have been recently reported by Iraqi study, but molds were the most encountered allergen in AS and AR

patients [13]. Although most studies reported that the specific IgE measurement was of great value in determining AS and AR or their severity, the distribution of the type of allergen that triggered the IgE antibody was different between the studies. This difference is related to the fact that IgE antibody levels are influenced by the environmental allergens in terms of amount and nature [24]. In addition, other factors may have an effect; for instance age, gender, ethnicity, and genetic factors, as well as geographical conditions [25-27].

Conclusions

This study confirmed the predictive significance of IgE in AS and AR. This significance was not influenced by age, gender, or allergen type. However, the study was limited by the low sample size of AS and AR patients and controls, and it is certain that larger numbers of patients and controls will shed more light on the role of total and specific IgE in the pathophysiology of both allergies

Conflict of interest: The authors declare that there is no conflict of interest.

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