ORIGINAL ARTICLE

Relationship Between Serum Total IgE and Disease Severity in Patients With Allergic Asthma in Spain

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Abstract

Objectives: To evaluate the association between serum total IgE levels and disease severity in adult patients with persistent allergic asthma and to explore the main predictors of IgE levels.
Methods: We performed a multicenter, retrospective, observational study including adult patients diagnosed ≥1 year previously with persistent allergic asthma who were positive to ≥1 allergen. Patients also had serum total IgE and spirometry results available from the previous 12 months. Inclusion was stratified by asthma severity according to the GEMA 2009 criteria.
Results: We included 383 patients with allergic asthma (129 mild, 82 moderate, and 172 severe). Mean (SD) age was 38 (15), 46 (16), and 45 (15) years, respectively (*P*<0.001). Serum total IgE levels varied markedly (coefficient of variation, 147%). No association was observed with forced expiratory volume in 1 second (FEV_1) or asthma severity: mean (SD)/median (IQR) of 403 (616)/214 (108-409), 361 (516)/204 (126-361), and 473 (676)/211 (98-545) IU/mL in the mild, moderate, and severe subgroups, respectively (*P*=.951). The severe subgroup had a higher percentage of patients with >400 IU/mL (36% vs 26.4% [mild] and 18.3% [moderate], *P*=.010). In a multivariate multiple regression model, the independent predictors of higher IgE were younger age (*P*=.004), sensitization to ≥2 allergens (*P*=.009), male gender (*P*=.025), and family history of asthma (*P*=.122).
Conclusion: Serum total IgE levels in adult patients with persistent allergic asthma were high (two-thirds with levels >150 IU/mL) and extremely variable. We did not find a significant association between serum total IgE levels and asthma severity or airflow limitation, except for a higher percentage of patients with IgE >400 IU/mL in the severe subgroup.

Key words: IgE. Adult asthma. Asthma severity

Resumen

Objetivos: Evaluar la asociación entre los niveles séricos de IgE total y la gravedad de la enfermedad en adultos con asma alérgica persistente, y explorar los principales factores predictores de los niveles de IgE total.
Métodos: Estudio multicéntrico, observacional, retrospectivo que incluyó pacientes adultos diagnosticados de asma alérgica persistente al menos de un año de evolución, con positividad para ≥1 alérgeno, y que dispusieran de resultados de IgE sérica total y espirometría de los últimos 12 meses. Se estratificó la inclusión según la gravedad del asma, de acuerdo a los criterios GEMA 2009.
Resultados: Se incluyeron 383 pacientes con asma alérgica, 129 leve, 82 moderada y 172 grave, con una edad media (DE) de 38 (15), 46 (16) y 45 (15) años, respectivamente (p<0,001). Se observó una gran variabilidad en los niveles séricos de IgE total (coeficiente de variación 147%). No se observó asociación con el FEV_1 o la gravedad del asma: media (DE)/mediana (Q1, Q3) de 403 (616)/214 (108-409), 361 (516)/204 (126-361) y 473 (676)/211 (98-545) UI/mL en los subgrupos de asma leve/moderada/grave, respectivamente (*P*=0,951). El subgrupo grave presentó un mayor porcentaje de pacientes con IgE>400 UI/mL (36% frente a 26,4% (leve) y 18,3% (moderada) ,*P*=0,010). En un modelo de regresión múltiple multivariante, los predictores independientes de niveles más elevados de IgE fueron: una menor edad (*P*=0,004); la sensibilización a ≥2 alérgenos (*P*=0,009); el sexo masculino (*P*=0,025) y los antecedentes familiares de asma (*P*=0,122).

Conclusión: Los niveles séricos de IgE total en pacientes adultos con asma alérgica persistente fueron elevados (dos tercios con niveles >150 UI/mL) y extremadamente variables, y no se asociaron a la gravedad del asma ni a la limitación del flujo aéreo, a excepción de un mayor porcentaje de pacientes con IgE>400 UI/mL en el asma grave.

Palabras clave: IgE. Asma del adulto. Gravedad del asma

Introduction

Asthma is a chronic respiratory disease characterized by episodes of impaired breathing. In allergic asthma, IgE is the main cause of the allergic inflammatory reaction, participates in bronchial obstruction, and has a role in allergic asthma exacerbations [1].

One of the main goals of asthma management is to identify the factors associated with impaired disease control at early stages in order to initiate therapy aimed at long-term control. In this regard, several studies [2] have assessed the relationship between severity of allergic asthma and markers of atopy and inflammation, both in children [3] and in adults [4]. Since the identification and initial description of IgE by Ishizaka et al [5] in 1966 and Johansson and Bennich [6] in 1967, knowledge of the role of IgE in the pathogenesis of allergic diseases has increased considerably [7]. In 2005, Borish et al [8] reported that high levels of total IgE were associated mainly with moderate and severe asthma, especially in younger patients and in adults whose asthma began in childhood. Naqvi et al [2] found an inverse relationship between total IgE levels and lung function and, therefore, the severity of asthma in 3 different ethnic groups. However, these findings are not consistent across studies [2,9-11].

Based on the above observations, the aims of this study were to evaluate the association between serum total IgE levels and disease severity in adult patients with persistent allergic asthma and to explore the main predictors of IgE levels in these patients.

Methods

Participants

The study population comprised adult patients attending allergy or respiratory specialist clinics who had been diagnosed more than 1 year previously with persistent allergic asthma. To qualify for inclusion, patients had to be positive to at least 1 allergen, either in the skin prick test or by specific IgE measurement. In addition, the results of serum total IgE determination and spirometry performed within the previous 12 months had to be available in the patient's file. Patients with active diseases involving high IgE serum levels (ie, myeloma, parasitosis, and atopic dermatitis) were excluded from the study. Patients whose IgE levels had been measured during treatment with any anti-IgE therapy (omalizumab or immunotherapy) were also excluded (except if IgE had been determined prior to treatment initiation).

The study was conducted according to the Declaration of Helsinki, and the local ethics committees approved the protocol. All patients signed the informed consent prior to their participation.

Study Design

This study was a multicenter, retrospective, observational, cross-sectional study conducted in Spain with the participation of 65 specialists (allergists and respiratory medicine). Each investigator included approximately 9 patients, who were stratified according to asthma severity (3 mild, 3 moderate, and 3 severe [physician's criteria]) and to the therapy necessary for the patient to achieve control, as defined in the Spanish Guide for Asthma Management (GEMA) 2009 (Table 1) [1]. Data were retrospectively collected from patient files between November 2010 and March 2011. Relevant information included demographics, medical history, symptoms, health resource utilization due to asthma within the previous year, spirometry results, serum total IgE levels, specific IgE levels, skin prick test results, and current asthma treatments.

Statistical Analysis

The sample size was calculated to detect a minimal difference of 150 IU/mL in serum total IgE (assuming an SD of 400 IU/mL) between the 3 subgroups with 80% power and a .05 significance level. With these assumptions, the required sample size was 112 patients per group, to which we added 10% to cover incomplete/nonevaluable data. The final sample size was 375 individuals. Comparisons were made using an unpaired *t* test or nonparametric equivalent.

Descriptive statistics were obtained for all variables. Continuous variables were summarized as mean (SD) or median (IQR) and range. Absolute and relative frequencies were calculated for categorical variables. Results were presented for the overall sample and for the subgroups defined according to the severity criteria of GEMA 2009. Patients were classified into the 3 subgroups as follows. First, we classified patients according to information about drug therapies at inclusion collected in the case report form (GEMA 2009 criteria, Table 1), independently of the physician's classification. Second, we compared the physician's classification and the classification according to current treatment. Since we observed that physicians underestimated severity in 23% of cases and overestimated severity in 13%, we decided that it was more appropriate to base the classification on the information collected, rather than the classification reported by the physician.

Specific allergens were grouped into the following categories: mites (*Dermatophagoides pteronyssinus, Dermatophagoides farinae, Lepidoglyphus destructor*); pollen (cypress, planetree, olive, grass mixture, mugwort, and

Table 1. Criteria Used to Discriminate Between Mild, Moderate, and Severe Asthma in Treated Patients (GEMA 2009)[a]

	Minimum *maintenance* treatment requirements to achieve control
Mild	Stage 2 (monotherapy with low-dose inhaled corticosteroid or antileukotriene)
Moderate	Stage 3 (combination therapy with low-dose inhaled corticosteroid + long-acting β_2-adrenergic agonist or monotherapy with moderate-dose inhaled corticosteroid or combination therapy with low-dose inhaled corticosteroid + antileukotriene) or Stage 4 (combination therapy with moderate-dose inhaled corticosteroid + long-acting β_2-adrenergic agonist or moderate-dose inhaled corticosteroid + antileukotriene)
Severe	Stage 5 (combination therapy with high-dose inhaled corticosteroid + long-acting β_2-adrenergic agonist with or without antileukotriene and/or theophylline and/or omalizumab) or Stage 6 (combination therapy with high-dose inhaled corticosteroid + long-acting β_2-adrenergic agonist + oral corticosteroid with or without antileukotriene and/or theophylline and/or omalizumab)

[a]Therapy as needed with short-acting β_2-adrenergic agonists was not taken into account for the classification, since it can be administered at all stages.

Parietaria and *Salsola* species); epithelia (cat and dog); and fungi (*Alternaria, Cladosporium, Aspergillus*, and *Penicillium* species).

Continuous variables were compared using 1-way analysis of variance or the Kruskal-Wallis test; categorical data were compared using the chi-square test or Fisher exact test. For comparison purposes and multivariate analyses, IgE levels were normalized using log transformation. The relationship between IgE levels and age was analyzed using the Spearman correlation coefficient.

A multivariate multiple regression model was constructed to predict log-transformed IgE levels. We first tested the univariate relationship between total IgE and all the variables collected. Those with a *P* value <.20 in the univariate analyses were entered in the model and selected using a stepwise procedure.

P<.05 was considered significant. The SAS statistical package, version 9.1 (SAS Institute Inc.) was used for all the analyses.

Results

Patient Characteristics

A total of 383 patients (mild asthma, 129; moderate asthma, 82; and severe asthma, 172) were included in the study. Table 2 shows the main sociodemographic and clinical characteristics according to disease severity. Patients with mild asthma were younger, had earlier onset of asthma, and tended to have a lower BMI and higher degree of physical activity. No differences were observed between the subgroups in the number or distribution of allergens or in the percentage of patients with a family history of asthma or residence in coastal regions. Patients in our study were mainly allergic to mites (22.5%, n=86), pollen (20.4%, n=78), mites+pollen (11.7%, n=45), and mites+epithelia+pollen (9.7%, n=37).

As expected, the degree of airflow limitation and the number of exacerbations and related health resource utilization increased progressively with disease severity. Of note, 61% of patients with severe asthma were classified in this category owing not to reduced pulmonary function (≤60%), but to the frequency of their symptoms and/or exacerbations.

Distribution of Serum Total IgE Levels

Serum total IgE levels varied considerably in the study population (coefficient of variation, 147%). A right-skewed distribution was observed, with values ≤213 IU/mL (median) for 50% of patients and values >444 IU/mL for 25% of patients (75th percentile) (Table 3).

Association Between Serum Total IgE and Asthma Severity

Table 3 and Figure 1 show the distribution of serum total IgE levels in the 3 subgroups. The mean levels tended to be

Table 2. Sociodemographic and Clinical Characteristics of Patients With Persistent Allergic Asthma in Spain According to Disease Severity[a,b]

	Mild Asthma (n=129)	Moderate Asthma (n=82)	Severe Asthma (n=172)	Total (N=383)	*P* Value[c]
Age, years	38.5 (15.4)	46.3 (16.5)	44.7 (14.7)	43.0 (15.6)	<.001
Female, No. (%)	72 (55.8)	50 (61.0)	100 (58.1)	222 (58.0)	.672
BMI, kg/m²	26.1 (4.9)	26.8 (4.5)	27.2 (5.3)	26.8 (5.0)	.137
Overweight, No. (%)	33 (25.6)	32 (39.0)	61 (35.5)	126 (32.9)	
Obesity, No. (%)	28 (21.7)	20 (24.4)	46 (26.7)	94 (24.5)	
Physical activity, No. (%)					.051
High	27 (20.9)	13 (15.9)	24 (14.0)	64 (16.7)	
Intermediate	57 (44.2)	32 (39.0)	59 (34.3)	148 (38.6)	
Low	43 (33.3)	37 (45.1)	88 (51.2)	168 (43.9)	
Frequent alcohol intake, No. (%)	5 (3.9)	1 (1.2)	9 (5.2)	15 (3.9)	.305
Active smoking, No. (%)	16 (12.4)	6 (7.3)	8 (4.7)	30 (7.8)	.048
Age of onset of asthma, y	26.2 (16.1)	30.0 (17.1)	30.9 (16.9)	29.1 (16.7)	.039
Family history of asthma, No. (%)	49 (38.0)	31 (37.8)	79 (45.9)	159 (41.5)	.263
Coastal region, No. (%)	63 (55.8)	39 (51.3)	99 (61.9)	201 (57.6)	.275
Number of allergens, No. (%)					.702
1	33 (25.6)	23 (28.0)	40 (23.3)	96 (25.1)	
≥ 2	96 (74.4)	59 (72.0)	132 (76.7)	287 (74.9)	
FVC, No. (%)					<.001
<60%	0 (0%)	1 (1.2%)	30 (17.4%)	31 (8.1%)	
60-80%	4 (3.1%)	23 (28.0)	70 (40.7%)	97 (25.3%)	
>80%	125 (96.9%)	58 (70.7%)	72 (41.9%)	255 (66.6%)	
FEV_1, No. (%)					<.001
<60%	0 (0.0%)	0 (0.0%)	67 (39.0%)	67 (17.5%)	
60-80%	0 (0.0%)	58 (70.7%)	60 (34.7%)	118 (30.8%)	
>80%	129 (100%)	24 (29.3%)	45 (26.2%)	198 (51.7%)	
Exacerbations in the last year, median (IQR)	0 (0-1)	1 (0-3)	3 (2-4)	2 (0-3)	<.001
Health resource utilization (during the last year) due to asthma:					
Corticosteroid treatment rounds	0.3 (0.8)	0.9 (1.3)	2.6 (3.6)	1.4 (2.8)	<.001
Visits to emergency room	0.2 (0.5)	0.7 (1.5)	2.6 (5.8)	1.4 (4.1)	<.001
Hospitalizations	0.0 (0.1)	0.0 (0.2)	0.2 (0.6)	0.1 (0.4)	<.001
Unscheduled visits	0.6 (1.0)	1.5 (2.1)	4.0 (6.8)	2.3 (4.9)	<.001

Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.
[a]Continuous values expressed as mean ± SD, except otherwise indicated.
[b]Number of patients with missing data in mild/moderate/severe asthma (n/n/n) subgroups: age (1/0/0), gender (1/2/1), BMI (1/0/1), physical activity (2/0/1), frequent alcohol intake (0/0/0), active smoking (0/2/1), age of onset of asthma (3/2/7), family history of asthma (0/0/1), geographical region (16/6/12), number of allergens (0/0/0), FVC (0/0/0), FEV_1 (0/0/0), exacerbations in the last year (0/0/0), steroid treatment rounds (1/2/5), visits to the emergency room (1/0/4), hospitalizations (1/1/6), and unscheduled visits (1/1/4).
[c]Analysis of variance or Kruskal-Wallis test for continuous variables and chi-square test for categorical variables.

higher in severe asthma, but the median levels and coefficients of variation were comparable. Overall, the distribution of the variables did not differ significantly between the 3 subgroups (*P*=.951). However, a significantly higher percentage of patients with levels >400 IU/mL was found in the severe subgroup (*P*=.010, Figure 2), whereas no differences were observed in the number of patients with levels <150 IU/mL (*P*=.842).

Association Between Serum Total IgE and Pulmonary Function

Figure 3 shows the distribution of serum total IgE levels according to pulmonary function as measured by forced expiratory volume in 1 second (FEV_1) (<60%, n=67; 60%-80%, n=118; and >80%, n=198). Although a trend towards higher levels was observed in patients with an FEV_1 <60% (mean

Table 3. Variability in Serum Total IgE Levels According to Asthma Severity

	Mild Asthma (n=129)	Moderate Asthma (n=82)	Severe Asthma (n=172)	Total (N=383)
Mean (SD)	403 (616)	361 (516)	473 (676)	425 (624)
Median (IQR)	214 (108-409)	204 (126-361)	211 (98-545)	213 (107-444)
Coefficient of variation[a]	153%	143%	143%	147%
Serum total IgE, IU/mL, No. (%)				
<150 IU/mL	46 (35.7)	31 (37.8)	67 (39.0)	144 (37.6)
150-400 IU/mL	49 (37.9)	36 (43.9)	43 (25.0)	128 (33.4)
>400 IU/mL	34 (26.4)	15 (18.3)	62 (36.0)	111 (29.0)

[a]Calculated as SD divided by mean and multiplied by 100.

[95%CI], 546 [340-751] for patients <60%; 351 [277-425] for 60%-80%; 429 [339-519] IU/mL for >80%), the differences were not statistically significant (*P*=.252).

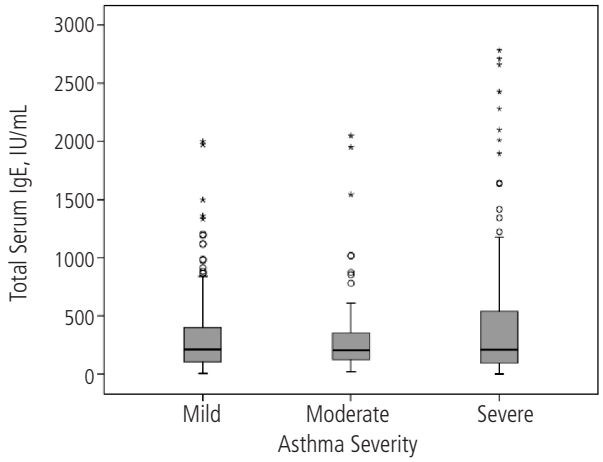

Figure 1. Serum total IgE levels according to asthma severity. The box plots span data values between the first and third quartiles. The dark horizontal line within the box represents the median. The upper and lower fences represent the value equal to the 75th and 25th percentiles ±1.5 times the interquartile range.

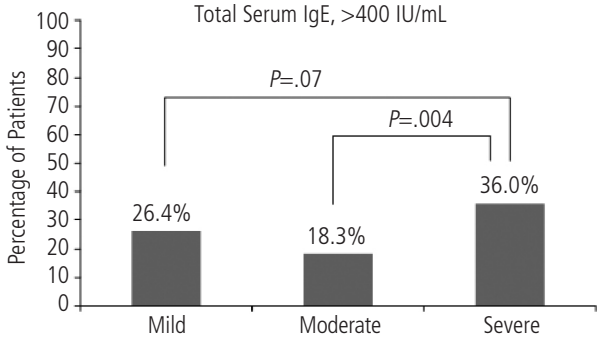

Figure 2. Percentage of patients with serum total IgE >400 IU/mL according to asthma severity (chi-square test, overall *P* value = .010).

Factors Associated With Serum Total IgE Levels

A significant and negative correlation was observed between age and IgE level (Figure 4). However, this relationship varied depending on the presence of hereditary factors: when patients with and without a family history of asthma were analyzed separately, a significant correlation was only detected in the former (Spearman correlation coefficient, r=–0.240, *P*<.001 in patients with a family history vs r=–0.066, *P*=.412 in patients with no family history). Patients with a family history tended to be younger (41.0 [15.2] vs 44.2 [15.8] years; *P*=.061) and had earlier onset of disease (27.7 [17.4] vs 30.7 [16.8] years; *P*=.166).

Figure 5 shows the relationship between IgE levels and sociodemographic and clinical variables. No significant differences were found for any of them, except for the number of allergens: patients with ≥2 allergens had higher total IgE levels than patients who were positive to only 1 allergen (*P*=.002). A trend towards higher levels was also observed in male patients, those living in inland regions, those with

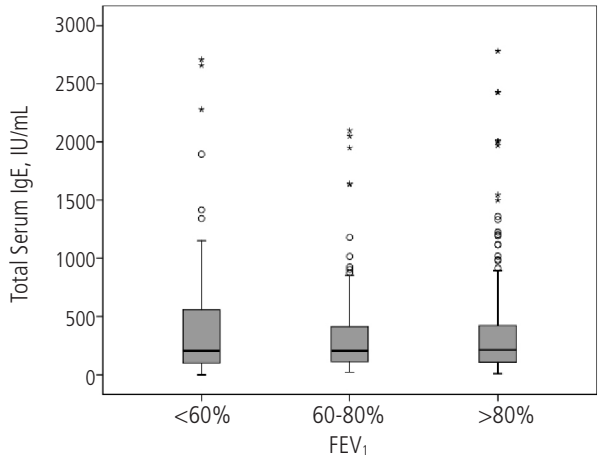

Figure 3. Serum total IgE levels according to FEV_1. The box plots span data values between the first and third quartiles. The dark horizontal line within the box represents the median. The upper and lower fences represent the value equal to the 75th and 25th percentiles ±1.5 times the interquartile range. FEV_1 indicates forced expiratory volume in 1 second.

≥2 exacerbations in the last year, and those with a family history of asthma. Similarly, no differences were observed between patients monosensitized to pollen and patients monosensitized to mites (data not shown).

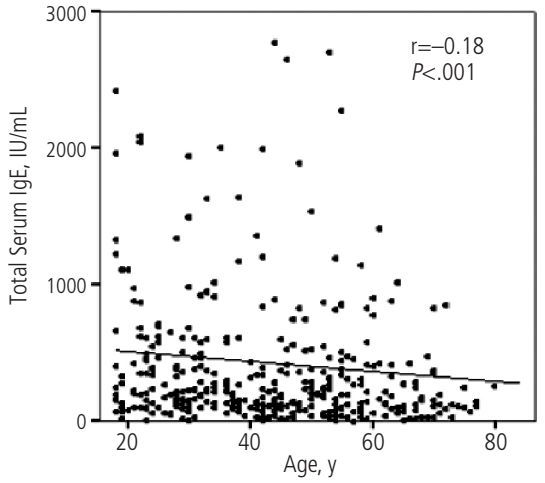

Figure 4. Relationship between serum total IgE levels and age (r=Spearman correlation coefficient).

In the multivariate multiple regression model with log-transformed IgE as the dependent variable, the main independent predictors of higher serum total IgE levels in patients with persistent allergic asthma were as follows: younger age (estimated effect [SE] of 0.005 [0.002] units more of log-transformed IgE for each year, *P*=.004); ≥2 allergens (0.158 [0.060] units more of log-IgE vs 1 allergen, *P*=.009); male gender (0.118 [0.052] units more of log-transformed IgE vs females, *P*=.025); and family history of asthma (0.082 [0.053] units more of log-transformed IgE vs patients with no family history, *P*=.122). However, the overall percentage of variability in serum total IgE explained by these variables was modest (7%). Other variables tested and not included in the final model were body mass index, asthma severity, FEV_1, forced vital capacity, number of exacerbations in the last year, number of corticosteroid courses, and age at asthma onset.

Discussion

We analyzed the relationship between serum total IgE levels and disease severity in a large cohort of unselected adult patients with persistent allergic asthma. We failed to replicate the previously reported direct association between these 2 variables and between total IgE and FEV_1 [2,9-11]. One possible explanation for this finding is that the IgE

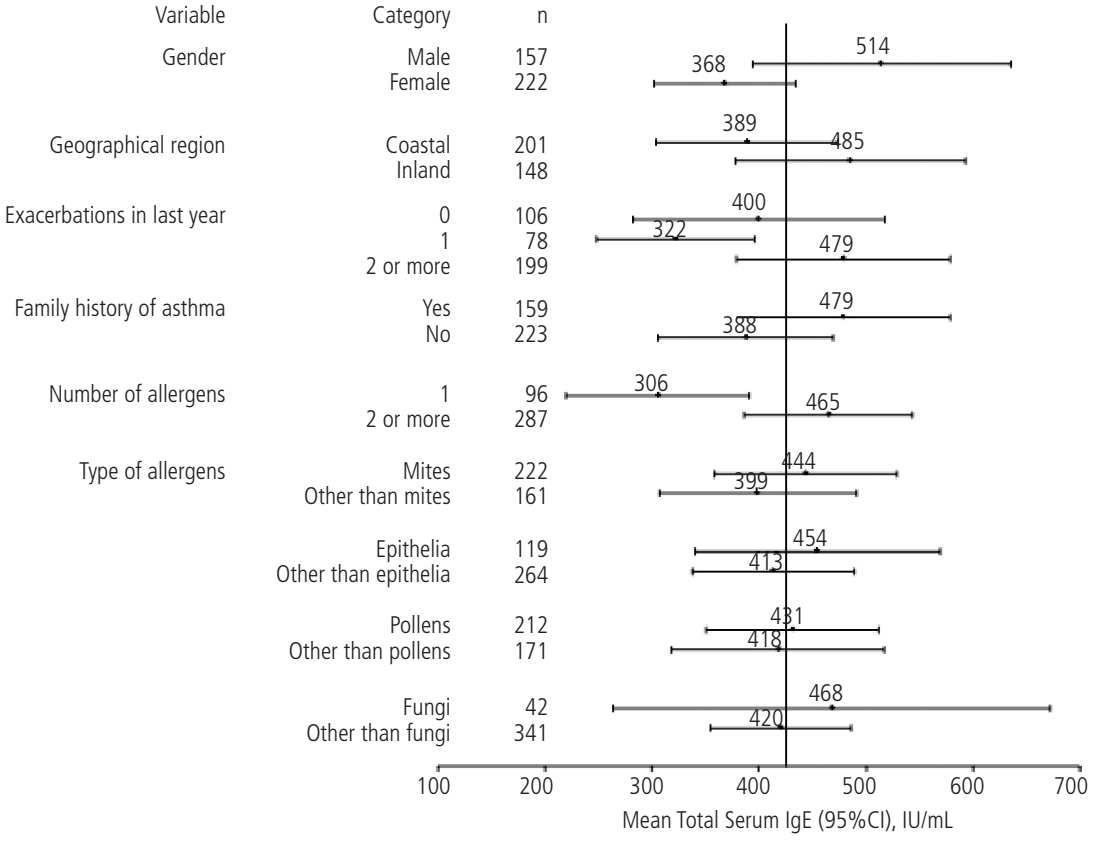

Figure 5. Relationship between serum total IgE and various sociodemographic and clinical variables.

levels in our cohort, which was composed exclusively of allergic patients, were relatively high compared to those from previous studies [8,10]. In the large prospective study from de Marco et al [14], the mean levels of IgE at baseline in the subgroups with moderate or severe asthma were around 130 IU/mL, much lower than the levels of around 400 IU/mL detected in our sample. The authors observed that these "high" levels were associated with early deterioration of pulmonary function, together with persistent cough or mucus hypersecretion, and concluded that the development of severe asthma could be predicted.

We found wide variability between the 3 subgroups, suggesting that IgE is subject to intrinsic variability, which is not necessarily asthma-related. These major interpatient differences had already been described [15], as had wide intrapatient variability over time [16]. Although we did not find a significant association between total IgE and the 3 stages of asthma severity, a higher percentage of patients with IgE >400 IU/mL was observed in patients with severe asthma. Thus, our results indicate that a cut point of 400 IU/mL could be predictive of more severe, difficult-to-treat asthma.

When we explored factors associated with IgE levels in these patients, we were not able to explain much of the observed variability. Although a trend towards higher levels was observed in patients living in inland regions with ≥2 exacerbations in the previous year and a family history of asthma, none of these variables remained significant in the multivariate analysis. The only 3 independent predictors of higher levels of IgE were younger age (especially in patients with a family history of asthma), reactivity to ≥1 allergen, and male gender. These 3 variables had been reported elsewhere [17,18]. The lack of association with other reported factors, such as active smoking or alcohol intake, could be explained by the low percentages of patients with these 2 habits in our cohort. In addition, active diseases that are affected by IgE levels (ie, myeloma, parasitosis, and atopic dermatitis) were excluded from the study.

Borish et al [8] found that high levels of total IgE were associated more with moderate and severe asthma (subjectively categorized), especially in younger patients and in adults whose asthma began in childhood. The relationship with younger age in patients with a family history of asthma suggests that increased IgE level is partly genetically determined and that in patients with inherited susceptibility to asthma, levels decrease progressively with age, possibly owing to the confounding effect of diminished allergic sensitization, one of the key factors that influence IgE levels and whose prevalence clearly decreases with age [19].

Our study is subject to a series of limitations. Retrospective data collection could be associated with residual confounding owing to missing data, recall bias, and other types of measurement error. Some patients could have been misclassified into a lower disease severity subgroup. Although most patients (94%) were being treated at inclusion and severity was therefore correctly assessed according to the therapy administered, we cannot rule out the possibility that some patients with severe disease were misclassified into the mild or moderate subgroups in cases of poor asthma control and undertreatment in clinical practice (which, in Spain, can affect around 50% of patients [12,13]). Because of the observational design, IgE and pulmonary function were not necessarily measured simultaneously. Although we did not find seasonal differences in total IgE levels in the total sample or in the subgroup of patients with pollen allergy (data not shown), we cannot rule out a bias in our results due to the presence of delayed measurements. It is also probable that some of the factors involved in the complex regulation of total IgE levels were not accounted for. Although we considered age, gender, smoking, alcohol consumption, and number of allergens registered in the patient's file, we cannot rule out the presence of other major determinants, such as additional allergens, active infections, or family history of atopy. Accordingly, our results must be interpreted with caution.

In conclusion, serum total IgE levels in adult patients with persistent allergic asthma from Spain were high (two-thirds with levels >150 IU/mL) and varied considerably. We did not find a significant relationship with disease severity or degree of airflow limitation, except for a higher percentage of patients with IgE >400 IU/mL in the subgroup with severe asthma. Male gender, younger age (especially in patients with a family history of asthma), and ≥1 allergen were associated with higher levels. The marked variability observed in serum total IgE prevents it from being used as a marker of asthma severity, although a cut point of 400 IU/mL could be suggestive of more severe, difficult-to-treat asthma.

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Conflicts of Interest

At the time of writing, Lys Herráez was an employee of Novartis Farmacéutica, SA.

Previous Presentation

Data from the study were presented at the European Academy of Allergy and Clinical Immunology (EAACI) Congress in 2013 and at The Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) Congress in 2013.

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