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Prevalence of Sensitization to Panallergens and IgG4 Profiles Against Specific Foods in Patients with Allergic-Phenotype Eosinophilic Esophagitis

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Abstract

Background: Eosinophilic esophagitis (EoE) pathophysiological mechanism is complex and it s still being investigated. We believe there is a group of patients with eosinophilic esophagitis which we could differentiate as having an allergic phenotype, who exhibit a sensitization profile (aeroallergens, panallergens, foods and specific IgG4 levels) with significant differences when compared to patients with conventional allergic disease without associated eosinophilic esophagitis and healthy controls. Method: We have measured the prevalence of sensitization to aeroallergens, foods and panallergens by means of molecular diagnostic techniques (ImmunoCAP^{TM} ISAC) and determined the levels of specific IgG4 against foods and eosinophilic derived neurotoxin (EDN) (ImmunoCAP technology) in patients with EoE of allergic phenotype to study if there are statistically significant differences with respect to the control groups (patients with different allergic pathologies without EoE and healthy patients without documented allergies). The total number of patients under study was 118, distributed among the different study groups. The case group (Allergic phenotype EoE patients) has 48 subjects. The food and respiratory allergy control groups, 30 subjects each. Finally, we included 10 in the healthy control group. Results: We were able to identify statistically significant differences when comparing levels of food-specific IgG4. Milk, egg, wheat, nuts, soy, cod, and LTP stood out. We did not observe significant differences in relation to sensitization to aeroallergens, foods, or panallergens. We also did not observe differences in EDN levels. Conclusion: We present a study in which statistically significant differences in IgG4 levels were observed in response to different types of food, comparing patients with eosinophilic esophagitis of allergic phenotype (case group) against subjects with allergic pathology without EoE and healthy subjects (control groups). Determining whether the detected foods are clinically relevant or not in these patients would be fundamental to establishing their usefulness as a treatment alternative in our patients.

Keywords: eosinophilic esophagitis; food allergy; IgG4; EDN

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1. Introduction

A multidisciplinary approach to studying this disease is essential. The clinical and research work carried out by specialists in gastroenterology, allergists, and/or pediatricians as well as other specialists in this disease, has enabled progress in important areas such as epidemiology, diagnosis and treatment [3–5].

Although current guidelines have dismissed the use of classic allergy tests (IgE-mediated) to define certain treatments such as diets, their use plays an important role in the phenotyping of these patients, reporting a nearly 80% prevalence of sensitization to foods and/or aeroallergens in patients with EoE [6,7]. Distinct histopathological patterns (inflammatory, stenotic and mixed), which are not mutually exclusive, have been described [8,9].

In recent years, diagnosis in allergology has been progressing considerably. Currently, in routine clinical practice, we employ advanced techniques that enable precise diagnosis. Molecular diagnostics (ImmunoCAP™ ISAC) has been particularly helpful in the field of food allergy and immunotherapy. For example, the detection of allergy to panallergens (antigens present in taxonomically related or unrelated species) explains numerous cross-reactivity phenomena between foods and aeroallergens. These phenomena and sensitization to panallergens may be relevant in patients with allergic-phenotype EoE [10,11]. It is very important to highlight the high level of sensitization observed in patients with EOE and the simultaneous presence of Th2 profile pathologies.

On the other hand, although the use of specific IgG4 in the diagnosis of common food allergy has been dismissed, there are publications showing statistically significant differences in specific IgG4 levels of this subtype when comparing patients with eosinophilic esophagitis to other allergic or healthy individuals [12,13]. It could be a useful non-invasive diagnostic tool in EOE patients.

The EOE-3 project is part of a research line aimed at improving our understanding of the allergic phenotype in patients with eosinophilic esophagitis and at studying tools for its diagnosis and management.

We believe there is a group of patients with eosinophilic esophagitis which we could differentiate as having an allergic phenotype, who exhibit a sensitization profile (aeroallergens, panallergens, foods and specific IgG4 levels) with significant differences when compared to patients with conventional allergic disease without associated eosinophilic esophagitis and healthy controls.

OBJECTIVES:

MAIN

1. To determine the prevalence of sensitization to aeroallergens, foods, and panallergens (LTPs, TLPs, PR10, profilin and tropomiosin) using molecular diagnostic techniques (ImmunoCAP™ ISAC), to measure levels of food-specific IgG4 (ImmunoCAP technology) in patients with allergic-phenotype EoE and to assess whether there are statistically significant differences compared with control groups (patients with exclusively IgE-mediated immediate food allergy without EoE, patients with respiratory allergy without EoE, and healthy individuals with no documented allergies).

SECONDARY

1. To investigate whether there is a correlation between sensitization to panallergens/aeroallergens and seasonal exacerbations in patients with allergic-phenotype EoE.

2. To investigate whether there are statistically significant differences in EDN levels among the different study groups.

2. Materials and Methods

STUDY DESIGN:

Observational, prospective, case-control, multicenter study. The study was reviewed and approved by the ethics committee of the Elda general hospital (Alicante, Spain).

SAMPLE SELECTION:

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Patient selection was carried out during routine office visits. A total of 118 patients were selected (from all participating centers) for groups 1 (cases), 2, 3, and 4 (controls).

Group 1: patients with allergic-phenotype EoE (EoE objectively diagnosed according to clinical criteria dysphagia, chest tightness, food impactions, or other compatible symptoms and the histological criterion of >15 eosinophils per high-power field in a biopsy from at least one esophageal segment, along with at least one allergic condition: rhinitis, asthma, and/or atopic dermatitis), who are either not receiving any pharmacological treatment or are on proton pump inhibitors (PPIs) and/or inhaled-swallowed corticosteroids, but who are not following a food elimination diet for their EoE (at least during the 12 weeks or 3 months prior to the study).

Group 2: patients with IgE-mediated food allergy (type I mechanism). That is, patients who experience immediate symptoms, between 0 and 120 minutes after ingesting the food, with a clinical spectrum ranging from oral allergy syndrome to anaphylaxis. They may have other allergic diseases (rhinitis, asthma, or atopic dermatitis), but not EoE.

Group 3: patients with respiratory allergy but no food allergy and no EoE. These patients should not report any symptoms suggestive of allergy related to food intake.

Group 4: 10 healthy control patients with no documented allergies of any kind.

Patients under the age of 18, with hypereosinophilic syndrome, hematological disorders, immunodeficiencies, or oncological processes, undergoing treatment with immunosuppressants or biological therapies, or EoE patients with food elimination diets or following them in the 12 weeks or 3 months prior to the study and EoE patients who are undergoing allergen immunotherapy were excluded.

SAMPLING:

For convenience, based on the selection criteria, the sample size (n) is 118 patients from the various participating centers, to be distributed among the different study groups. Forty-eight EoE patients with aeroallergens and food allergic sensitization, 30 patients with IgE mediated food allergy, 30 patients with respiratory allergy without any food allergy or food-related symptoms, and 10 healthy controls were included.

SAMPLE SIZE:

Assuming we want an odds ratio of 4 or higher, it has been calculated that a sample size of 30 to 40 patients per group is sufficient (95% confidence level/80% statistical power).

STATISTICAL STUDY:

Descriptive analysis, by variable type. Proportion for the qualitative variable, and measures of central tendency (mean, mode, and median) and dispersion (standard deviation, standard deviation, and variance) for the quantitative variable. For the most relevant variables, 95% confidence intervals will be calculated.

In bivariate analysis, if the variable follows a normal distribution, parametric tests are used: chi-square to compare proportions and Student's t-test to compare means. If the variable does not follow a normal distribution, nonparametric tests will be used depending on the type of variable. Statistical significance is set at $p < 0.05$.

Multivariate analysis will be used to minimize confounding bias; depending on the dependent variable, multivariate analysis will be performed using stepwise binary logistic regression. As a measure of association, odds ratios will be calculated with their 95% confidence intervals. To assess the multivariate model's discriminatory ability, ROC curves will be calculated along with their areas under the curve and 95% confidence intervals.

As this is a case-control study, we will perform a binary multiple logistic regression analysis, expecting to obtain consistent crude and adjusted results. Three case-control studies will be conducted: 1st, GROUP 1 (CASES) versus GROUP 2 (CONTROLS WITH TYPICAL FOOD ALLERGY); 2nd, GROUP 1 (CASES) versus GROUP 3 (CONTROLS WITH ENVIRONMENTAL ALLERGY); and 3rd, GROUP 1 (CASES) versus GROUP 4 (HEALTHY CONTROLS).

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3. Results

Finally, a total of 118 subjects were enrolled in the study, and their distribution across the different groups is shown in Table 1. Sociodemographic characteristics in terms of age and sex are described in Tables 2 and 3. The age and sex distribution in the case/EoE group is consistent with previous reports [14].

Table 1. Sample disposition.

	n	%
Group 1/Cases: patients with allergic-phenotype EoE	48	40,67
Group 2: patients with IgE-mediated food allergy without EoE	30	25,4
Group 3: patients with respiratory allergy without food allergy or EoE	30	25,4
Grupo 4: healthy controls	10	8,5
Total subjects	118	100

Table 2. Sociodemographic characteristics: sex.

	Group 1		Group 2		Group 3		Group 4		Total	
	n	%	n	%	n	%	n	%	n	%
Men	31	64,6	10	33,3	13	43,3	3	33,3	57	48,3
Women	17	35,4	20	66,7	17	56,7	7	66,7	61	51,7
Total	48	100	30	100	30	100	10	100	118	100

Table 3. Sociodemographic characteristics: age.

	n	Minimum	Pct25	Mean	Median	Pct75	Maximum	Standard deviation
Group 1	48	17	30,3	37,8	35,0	46,0	66,0	12,5
Group 2	30	19	22,3	33,5	27,5	42,5	72,0	15,2
Group 3	30	20	31,0	41,6	42,0	50,0	65,0	12,5
Group 4	10	28	40,3	49,3	49,0	53,8	75,0	14,2
Total	118	17	27,0	38,7	37,0	48,8	75,0	13,9

Tables 4–6 show the IgE-mediated sensitization profiles of the different groups for foods, aeroallergens and panallergens.

Table 4. IgE mediated food sensitization.

	Group 1		Group 2		Group 3		Group 4		Total	
	N	%	N	%	N	%	N	%	N	%
No food sensitization	28	70,0	7	23,3	29	96,7	10	100,0	74	62,7
With food sensitization	12	30,0	23	76,7	1	3,3	0	0,0	44	37,3
Nuts	5	12,5	9	30,0					14	11,9
Fruits	10	25,0	9	30,0					19	16,1
Shellfish	1	2,5	4	13,3					5	4,2
Milk	4	10,0	3	10,0					7	5,9

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Egg	4	10,0	5	16,7	1	3,3			10	8,5
Fish	4	10,0	0	0,0					4	3,4
Wheat	4	10,0	5	16,7					9	7,6
Soy	2	5,0	7	23,3					9	7,6
Mussel	1	2,5	1	3,3					2	1,7
Cephalopods	1	2,5	1	3,3					2	1,7
Total	40	100	30	100	30	100	10	100	118	100

Table 5. IgE mediated aeroallergens sensitization.

	Group 1		Group 2		Group 3		Group 4		Total	
	N	%	N	%	N	%	N	%	N	%
No aeroallergens sensitization	2	5,0	1	3,3	0	0,0	6	20,0	9	7,6
With aeroallergens sensitization	38	95,0	29	96,7	30	100	4	97,5	109	92,4
Grasses	36	94,7	17	58,6	14	46,7	1	25,0	68	62,4
Olea europea	22	57,9	11	37,9	12	40,0	1	25,0	46	42,2
Salsola kali	8	21,1	1	3,4	5	16,7	0	0,0	14	12,8
Artemisia vulgaris	6	15,8	5	17,2	4	13,3	0	0,0	15	13,8
Cupressus arizonica	24	63,2	10	34,5	19	63,3	1	25,0	54	49,5
Betula	2	5,3	6	20,7	2	6,7	0	0,0	10	9,2
D. Pteronyssinus	17	44,7	8	27,6	5	16,7	0	0,0	30	27,5
D. Farinae	17	44,7	7	24,1	3	10,0	0	0,0	27	24,8
Dog epithelium	15	39,5	12	41,4	15	50,0	0	0,0	42	38,5
Cat epithelium	22	57,9	14	48,3	8	26,7	0	0,0	44	40,4
Alternaria alternata	12	31,6	7	24,1	4	13,3	1	25,0	24	22,0
Plantago	5	13,2	3	10,3	2	6,7	0	0,0	10	9,2
Platanus acerofila	2	5,3	0	0,0	2	6,7	0	0,0	4	3,7
Parietaria judaica	1	2,6	0	0,0	1	3,3	0	0,0	2	1,8
Total	40	100	30	100	30	100	10	100	118	100

Table 6. IgE mediated panallergen sensitization.

	Group 1		Group 2		Group 3		Group 4		Total	
	N	%	N	%	N	%	N	%	N	%
No panallergens sensitization	19	47,5	8	26,7	19	63,3	10	100	56	47,5
Panallergens sensitization	21	52,5	22	73,3	11	36,7	0	0,0	62	52,5
LTP	16	76,2	13	59,1	3	27,3	0	0,0	32	51,6
TLP	10	47,6	2	9,1	2	18,2	0	0,0	14	22,6
Profilin	9	42,9	9	40,9	4	36,4	0	0,0	22	35,5
PR10	2	9,5	6	27,3	3	27,3	0	0,0	11	17,7
Tropomiosin	3	14,3	5	22,7	0	0,0	0	0,0	8	12,9
CCD	6	28,6	3	13,6	7	63,6	0	0,0	16	25,8
Total	40	100	30	100	30	100	10	100	118	100

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The EoE group exhibited significantly higher levels of food-specific IgG4 to several foods, including wheat, peanut, soy, casein, cod, hazelnut, and almond, compared with control group 2 (Table 7). Compared to control group 3, there is a greater response in the EoE patient group for egg white, wheat, peanut, soy, casein, cod, walnut, hazelnut, almond, and Pru p3. In the case of cod, although there are significant differences, the effect size is small (0.020) (Table 8). The EDN levels observed were: Group 1 56.59 ng/mL±18.30; Group 2 60.19 ng/mL±19.81; Group 3 47.34ng/mL±18.21; Group 4 30.5ng/mL±17.45. In both cases, no significant differences were observed in EDN levels or in sensitization to panallergens. No significant differences were observed in food and aeroallergen sensitization when comparing group 1 with groups 2 and 3

Table 7. Differences between groups in EDN and IgG4 values (groups 1 and 2).

	p-value*	Effect**	IC95%
EDN	0,494	-5,865	-22,630-10,510
Egg white	**0,055**	1,230	-0,020-3,680
Wheat	**0,001**	0,900	0,300-1,640
Peanut	**0,015**	0,100	0,020-0,320
Soyben	**0,012**	0,050	0,010-0,140
Casein	**0,027**	0,770	0,030-2,770
Cod	**0,038**	0,010	0,000-0,030
Walnut	**0,055**	0,060	0,000-0,280
Hazelnut	**0,012**	0,170	0,020-0,370
Almond	**0,010**	0,320	0,030-0,740
Phl p12	0,291	0,010	-0,010-0,030
Bet v1	0,113	0,000	0,000-0,010
Pru p3	**0,057**	0,050	0,000-0,140
Pen a1	0,214	0,000	0,000-0,020

*P-value calculated using the Mann-Whitney test for nonparametric samples, with a 95% confidence level. ** Hodges-Lehmann median difference for independent samples.

Table 8. Differences between groups in EDN and IgG4 values (groups 1 and 3).

	p-value*	Effect**	IC95%
EDN	0,444	4,340	-9,370-18,070
Egg white	**0,007**	1,540	0,270-4,040
Wheat	**0,000**	0,970	0,410-1,660
Peanut	**0,004**	0,100	0,030-0,330
Soybean	**0,015**	0,050	0,010-0,160
Casein	**0,000**	1,375	0,490-4,320
Cod	**0,000**	0,020	0,010-0,040
Walnut	**0,008**	0,100	0,020-0,300
Hazelnut	**0,007**	0,185	0,030-0,370
Almond	**0,017**	0,215	0,010-0,720
Phl p12	0,714	0,000	-0,020-0,030
Bet v1	0,230	0,000	0,000-0,010
Pru p3	**0,027**	0,065	0,010-0,150
Pen a1	0,117	0,010	0,000-0,020

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*P-value calculated using the Mann–Whitney test for nonparametric samples, with a 95% confidence level. ** Hodges-Lehmann median difference for independent samples.

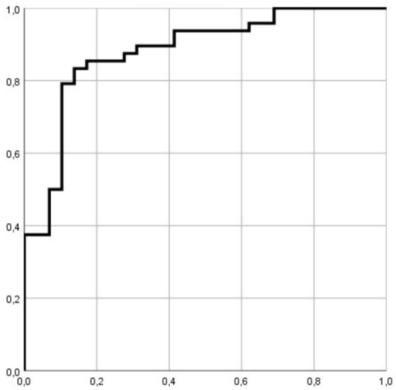
Comparing the case group with the control group of healthy subjects, there is a greater response in the allergic EoE patient group compared to group 4 for egg white, wheat, soy, casein, cod, walnut, hazelnut, Phl p12, Pru p3, and Pen a1. In the case of Pen a1, although there are significant differences, the effect size is small (0.010) (Table 9).

Table 9. Differences between groups in EDN and IgG4 values (groups 1 and 4).

	p-value*	Effect**	IC95%
EDN	0,387	7,525	-8,250-34,780
Egg white	0,032	2,300	0,130-6,520
Wheat	0,008	1,020	0,280-3,170
Peanut	**0,065**	0,100	-0,010-0,450
Soybean	0,010	0,060	0,010-0,410
Casein	0,003	1,580	0,200-6,650
Cod	0,001	0,030	0,010-0,060
Walnut	0,013	0,110	0,020-0,520
Hazelnut	0,007	0,260	0,030-0,850
Almond	0,703	0,050	-0,340-1,190
Phl p12	0,032	0,025	0,000-0,070
Bet v1	**0,084**	0,000	0,000-0,020
Pru p3	0,008	0,100	0,020-0,260
Pen a1	0,009	0,010	0,000-0,030

*P-value calculated using the Mann–Whitney test for nonparametric samples, with a 95% confidence level. ** Hodges-Lehmann median difference for independent samples.

Comparing the case group with control group 2, we observe that the model has good discriminative ability (> 0.8). It correctly distinguishes patients with EoE from the control group in approximately 88% of cases. The discrimination is statistically significant (the interval does not include 0.5 and p = 0.000), confirming that the model discriminates significantly better than chance (Figure 1).



Vertical axis: **sensitivity**; Horizontal axis: **specificity**.

Figure 1. ROC Curve. The optimal cutoff point, determined by the Youden index (J = 0.695), was set at a probability of 0.637, with sensitivity = 0.833 and specificity = 0.862, correctly classifying approximately 88% of cases.

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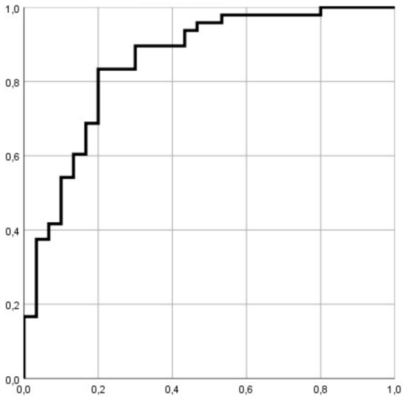
Comparing the case group with group 3, the model has good discriminative ability (> 0.8). It correctly distinguishes patients with EoE from the control group in approximately 85% of cases. The discrimination is statistically significant (the interval does not include 0.5 and p = 0.000), confirming that the model discriminates significantly better than chance (Figure 2).



Vertical axis: **sensitivity**; Horizontal axis: **specificity**.

Figure 2. ROC Curve. The optimal cutoff point, determined by the Youden index (J = 0.633), was set at a probability of 0.52, with a sensitivity of 0.833 and a specificity of 0.80.

The cutoff points for IgG4 levels observed when comparing groups 1 and 2 and groups 1 and 3 are shown in Tables 10 and 11.

Table 10. Cutoff points in the comparison of groups 1 and 2.

	Probability	Sensitivity	Especificity	Youdens index (J)
Wheat	0,365	0,875	0,483	0,358
Peanut	0,33	0,458	0,862	0,32
Soybean	0,295	0,354	0,931	0,285
Casein	0,79	0,646	0,69	0,336
Cod	0,025	0,625	0,69	0,315
Hazelnut	0,225	0,625	0,655	0,28
Almond	0,705	0,479	0,862	0,341

Table 11. Cutoff points in the comparison of groups 1 and 3.

	Probability	Sensitivity	Especificity	Youdens index (J)
Egg white	0,285	0,896	0,5	0,396
Wheat	0,915	0,688	0,767	0,455
Peanut	0,08	0,771	0,567	0,338
Soybean	0,47	0,313	0,967	0,28
Casein	0,635	0,688	0,8	0,488
Cod	0,025	0,625	0,833	0,458
Walnut	0,195	0,5	0,767	0,267
Hazelnut	0,135	0,688	0,633	0,321

It is important to note that IMMUNOCAP ISAC ® detected food allergy in 19 of the 48 patients in the EoE group (40%), whereas elevated IgG4 levels were observed in as many as 43 patients in this

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group (89%). Both techniques agreed on the detection of food allergy in 9 cases (21%), with wheat, egg white, and casein being the most commonly detected allergens. Although, in general, patients did not exhibit elevated IgG4 levels against panallergens, such levels were observed against LTPs in 12 of the 48 patients with EoE (25% of cases).

4. Discussion

We present a study in which statistically significant differences in IgG4 levels against different foods were observed when comparing patients with allergic-phenotype eosinophilic esophagitis (case group) with subjects with allergic disease but without EoE and healthy individuals (control groups).

Although the initial hypothesis posited the possibility of detecting differences in EDN levels or in the prevalence of sensitization to panallergens, no statistically significant differences were observed in this regard. It was only observed that EDN levels were higher in patients with allergic disease compared to those without documented allergy. We also did not observe any statistically significant differences in sensitization to aeroallergens or foods when comparing the groups of subjects with allergic disease.

In previous studies, significantly elevated specific IgG4 levels had been observed in EoE patients in response to foods such as wheat/gluten, milk, or egg [13,15]. In our study, we confirmed these foods and also observed significantly elevated levels regarding other foods such as nuts, soy, cod, or LTP. It is worth noting that these statistically significant differences are observed not only when compared with healthy controls, but also with patients with general allergic disease and food allergy without associated EoE.

As mentioned in the introduction, phenotyping in patients with EoE is essential to tailor management to each individual case. With regard to this phenotyping, identifying allergenic triggers is very important in allergic/Th2-type EoE profiles. The problem is that the immune response underlying the pathophysiological mechanism in EoE is complex. Currently, clinical guidelines have ruled out the exclusive use of IgE-mediated techniques to identify clinically relevant foods in patients with EoE. Therefore, going beyond IgE when evaluating these patients is essential.

In the present study, we confirm what was mentioned in the introduction regarding the potential role of IgG4 in identifying triggers in our patients. Compared to previous studies, we offer a larger sample size (n), comparisons across different groups, and a broader panel of potential triggers under investigation.

Once it has been confirmed that there are statistically significant differences between the various groups, it is important to establish the actual clinical relevance of the foods in which a significantly higher level is observed in the course of patients with allergic-phenotype EoE. Furthermore, the fact that there is some agreement between elevated Ig4 levels in response to certain foods and the foods identified as potential triggers by in vivo and in vitro IgE-mediated techniques reinforces that we could use IgE and no IgE-mediated techniques when evaluating our patients.

Conducting prospective studies with a sufficient number of patients to determine whether the identified foods are clinically relevant or not, based on the suggested combination of techniques, is the natural next step following the study that has been carried out. Additional studies are essential to clarify whether specific diets can become a useful alternative in the management of our patients. Currently, there is no evidence to that effect.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

Author Contributions: RGM and JDW conceived the study and drafted the manuscript. DGF performed the statistical analysis. RVM and JMR performed the immunological laboratory test. VJC, MTP, CCV, MAEA, IIC,MAGL and AAVB helped to draft the manuscript and participated in the study design. All authors read and approved the final manuscript.

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Institutional Review Board Statement: The study was assessed and approved by the IEC (Independent Ethics Committee) at the Elda General University Hospital.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data supporting reported results can be asked to corresponding author by email: joanwitek@yahoo.es.

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Abbreviations

The following abbreviations are used in this manuscript:

EoE	eosinophilic esophagitis
EDN	eosinophil derived neurotoxin
LTP	lipis transfer protein
IgE	inmunoglobulin E
IgG4	inmunoglobulin G4
PPI	proton pump inhibitords
TLP	thaumatin like proteins

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