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Study and Follow-Up of Patients with Allergic Eosinophilic Esophagitis Phenotype

Joan Doménech Witek*, Vicente Jover Cerdà, Zahira María Franzón Laz, Vanessa Aznar Tortonda, Ramón Rodríguez Pacheco, Isabel Maria Ontañon Timón, Marian Sellés Cutillas, Teresa Colomina Colomina

Hospital General de Elda, Sección de Alergología. H. Elda, Carretera de Sax, 03600, Elda, Alicante, Spain.
joanwitek@yahoo.es

***Corresponding Author:** Joan Doménech Witek, Hospital General de Elda. Sección de Alergología. Alicante. Spain.*

Abstract

Background: *Eosinophilic esophagitis (EoE) is a complex entity characterized by the variety of phenotypes and multiple management possibilities options with regard to diets and drugs. Recent publications discourage the prick test use or the specific IgE determination to detect food allergens in these patients. Our aim is to assess the EoE patients allergic sensitization profile and objectify the utility of ECP (eosinophilic cationic protein) or eosinophils in peripheral blood as an inflammation biomarkers for the follow-up of patients with EoE treated with specific diets, based on the hypothesis that we will observe a biomarkers decrease and clinical improvement after maintenance of these allergy test based diets.*

Methods: *37 patients diagnosed with EoE (25 males and 12 females) between January 2012 and June 2018, aged between 16 and 74 (38,83±14,55 years), were included consecutively. In all cases, we proceeded to perform prick test with extensive allergen batteries and specific IgE determination. Patients were assessed with results to recommend diets based on the tests performed and for serial biomarker determination.*

Results: *25 patients performed strictly the protocol of analytical extraction and the maintenance of the indicated diets, 24 of whom showed optimum response to specific diets based on allergy testing. A statistically significant difference ECP decrease and increase were observed in our patients with the food triggers withdrawal and reintroduction.*

Conclusion: *In our experience, there is an allergic phenotype of patients with EoE who can benefit from classic allergy tests, specific diets indication and biomarkers follow-up especially ECP. We believe that this profile of patients is similar in terms of evolution and response to patients with allergic asthma.*

Keywords: *Eosinophilic esophagitis, Eosinophil cationic protein, Specific diet, Food allergy.*

Introduction

Eosinophilic esophagitis (EoE) is a complex and exciting entity. It was initially described as an independent process in the 1990s. The first published articles that described this entity and its relationship with food allergy (Spergel 2002 and Sampson 2004) began to elucidate that EoE development is a mixed process with an IgE-mediated mechanism/non-IgE-mediated mechanism [1,2] and a certain sensitization profile to food allergens. It is striking that this disease has gone from having a low prevalence (40 to 50 cases per 100,000 inhabitants, possibly attributable to underdiagnosis) to 1 or 2 cases per 2,000 inhabitants in Europe and North America and up to 100 cases per 100,000 inhabitants in Spain [3,4,5]. The improved knowledge of the symptoms and sensitization profiles of our patients has made it possible to reduce underdiagnosis.

One of the fields in which the most progress has been made is the pharmacological and dietary management of our patients with EoE. Important researchers have markedly progressed EoE therapy with regard to pharmacological management protocols with proton pump inhibitors (PPIs) and inhaled or swallowed corticosteroids. Improvements in up to 50/60% of EoE patients treated exclusively with omeprazole have been observed [3]. With regard to diet, a great response to elemental diets and a very good response to diets of 6 foods (classified as the empirical type) have been observed [6,7]. The major problem with these diets is the patients quality of life loss, who are often unable to maintain such strict avoidance for an indefinite time. In this regard, diets based on allergy tests, which are less restrictive, are much more attractive to our patients. However, in the patients treated with these diets, the problem lies in the great variability in the improvement percentage observed (according to different studies, the improvement in response to these diets can range from 7% to 77%) [6]. This variability and poor reproducibility have led to the belief that diets based on allergy tests are not very useful in patients with EoE; these diets may have greater utility in the paediatric population [8,9].

Regarding disease follow-up and patient responsiveness to pharmacological treatment and/or a specific diets, the only objective way to check the possible reduction in oesophageal mucosa inflammation is by serial endoscopies with biopsy. To avoid subjecting patients to this invasive technique with risks and complications, several authors have tried to find inflammatory mediators such as total IgE, eosinophilic cationic protein (ECP) or peripheral blood eosinophils and have observed striking decreases but no statistical significance after the initiation of specific diets [10,11]. In the study carried out by our team prior to this study, we were able to identify a high percentage of sensitization to aeroallergens and foods in patients with EoE as well as a statistically significant ECP expression decrease after initiating specific diets based on allergy tests, avoiding confounding factors such as atopic dermatitis, active infections, dietary transgressions or seasonal respiratory symptoms. This decrease was correlated with clinical improvement in our patients and the possibility of abandoning pharmacological treatment [12].

The enormous variability in the detection of food allergens by skin tests and determinations of specific IgE levels reported by different publications and the data that have been described with respect to the response to specific diets, have led to the dismissal of the IgE response model for the EoE physiopathological mechanism [13]. In the aforementioned review, the authors established that the model that could explain this pathophysiological mechanism is similar to that observed in "contact dermatitis", a type IV mechanism mediated by T lymphocytes and characterized by a delayed response. The authors comment that anaphylaxis is not characteristic of the food allergies associated with EoE and that the exposure to aeroallergens (especially pollens) is not a trigger of episodes of exacerbation in patients with this disease. According to this review, another factor that shows that EoE is not an IgE-mediated disease is the poor response to omalizumab treatment. All these findings have led to the general recommendation to not use allergy tests (prick test, specific IgE measurements or microarrays) to detect food allergens in adult patients with EoE.

Our clinical practice experience is different. We have the impression that EoE is an entity that corresponds more to the asthmatic patient model as seen in previous publications [14]. We believe that these two entities (asthma and EoE) have in common the variety of phenotypes that we can find in routine clinical practice, including patients with an important atopic background with multiple sensitizations to environmental and food aeroallergens and others who have esophagitis with a non-allergic mechanism without any type of sensitization detected. It is evident that the profile of the patients referred to our practice corresponds to a greater extent to the allergic phenotype.

In conclusion, we set the following objectives:

1. Improve the knowledge of patients with EoE with an allergic phenotype in relation to the detection of food allergens, aeroallergens and panallergens; evolution in seasonal periods; and clinical improvement or worsening with the withdrawal or sequential reintroduction of foods.

2. To establish and analyse the usefulness of ECP and eosinophils in the peripheral blood as markers during the follow-up of patients with EoE treated with specific diets based on allergy test results.

We think that the ECP level and peripheral eosinophilia will decrease significantly after the establishment of the specific diets recommended after determining patient sensitization to foods by skin tests and/or specific IgE levels.

We hope that the anticipated decrease correlates with clinical improvement and with the possibility of abandoning symptomatic treatment with PPIs and/or inhaled/swallowed corticosteroids.

Methods

Study Design

This study included adult and adolescent patients referred by a digestive medicine specialist with an objective diagnosis of EoE, which was based on currently accepted metrics (15 or more eosinophils per oesophageal mucosal biopsy field) [15]. A total of 37 subjects were included between 1 January 2012 and 1 June 2018. During the initial appointment, relevant medical history information was gathered, and skin tests were performed with complete batteries of standard aeroallergens (23 items) and food allergens (62 items) (prick tests were performed using standardized allergen extracts from Bial Aristegui® Laboratories). Prick test with a diameter of 3mm or more were considered as positive. The patients were then referred to a hospital laboratory for a blood sample to be collected to establish the IgE levels specific to foods (minimum 32 items, ImmunoCAP Phadia 250), blood count and serum ECP level (baseline prior to establishing the specific diet). The patients were informed that the blood sample had to be collected when the subject had no respiratory symptoms compatible with rhinitis or asthma and no active infection; blood sample collection took place outside the relevant aggravation period in each patient (in relation to aeroallergen sensitization). Appointments were arranged for all patients to discuss the results of their tests and to recommend specific diets. We advised our patients to avoid foods when sensitivity had been detected by skin tests or specific IgE levels higher than 0.35 kUA/L as well as foods with cross-reactivity with pollens to which the patients were sensitized (mainly fruits and the Solanaceae family through allergic sensitization to profilins). After the diets had been established, appointments were arranged for the patients between 4 and 6 months later to assess the clinical response to the specific diet and to request a second blood sample for measuring blood counts and serum ECP levels to compare with the previous baseline values. When possible, we requested serial ECP levels and peripheral eosinophilia measurements in relation to the reintroduction of food triggers, always with intervals of 4 to 6 months. The characteristics of the patients included in the study with analytical values and endoscopic findings are summarized in Table 1.

Patients who did not follow the criteria of providing blood samples during a period without respiratory symptoms or outside of the aggravation period (the majority of samples were taken in August, December and January) were excluded. Furthermore, patients who had previously started diets prior to consultation were not included in the study.

Patients were told to continue with their symptomatic treatments as directed by their gastroenterologists for 2 to 3 months and then to stop treatment and continue only with the diets if they began to see improvements.

Histological and Endoscopic Studies

Endoscopic procedures were performed by an experienced gastroenterologist using a flexible 8.5 mm gastroscope with a 2.8 mm work channel (EG-530 FP, Fujinon, Fujifilm Corporation. Tokyo, Japan). Biopsies were performed using conventional forceps (Radial JawTM 4 Boston Scientific, Proparck, Costa Rica). No complications were observed as a result of the endoscopic procedures or biopsies. The histological study was performed only to have a confirmed diagnosis of EoE, not to carry out a control study after the maintenance of the indicated diets.

Biopsy specimens were sent to the Pathology Department, where they were fixed in formalin and embedded in paraffin. Serial sections were then cut using a microtome and stained with eosin and haematoxylin. EoE was diagnosed in sections with 15 or more eosinophils/high-power field (HPF) in at least one HPF.

Statistical Analysis

Comparisons were performed using non-parametric tests of paired samples. The post-diet measurements of each individual were compared to the baseline

measurements for the same individual. Continuous variables (ECP level and eosinophil count in the peripheral blood) are expressed as the mean ± SD values, and the Wilcoxon rank test was used to contrast hypotheses regarding pre- and post-diet continuous variables. Graphs show box plots with the median and interquartile range indicated.

Results

Epidemiological Data

Thirty-seven patients diagnosed with EoE (25 males and 12 females) between January 2012 and June 2018 and aged between 16 and 74 years (38.83 ± 14.55 years) were included consecutively. The epidemiological variables are summarized in Table 1.

Table 1. *Characteristics of the patients included in the study with analytical values and endoscopic findings.*

Number of patients	37
Men/Women	25/12 (69 %/31 %)
Age	38,83±14,55
Asthma	8 (21,62%)
Rhinoconjunctivitis	29 (78,37%)
Atopic dermatitis	2 (5,4%)
Aeroallergens	29 (78,37%)
Food allergies	33 (89,18%)
No allergic sensitizations	2 (5,4%)
Included in protocol	25 (67,56%)
Not included in protocol	12 (32,43%)
Overall clinical response to diet	
Improvement	24 (64,86%)
No response	1 (2,7%)
Not included	12 (32,43%)
Endoscopic findings	
Eosinophil in biopsies (n/hpf)	23,24±19,54
Inflammatory phenotype	17 (45,95%)
Stenosing phenotipe	20 (54,05%)
Analytical values	
Total IgE	334,80±320,26
ECP Pre diet (µg/mL)	33,71±19,40
Eosinophils Pre diet (periph. blood)	400±176,38

Clinical Data

Most of our patients had food sensitization. We objectified an atypical profile of food sensitization in adults, like allergies to gluten, rice, soy, egg and milk (food sensitizations are summarized in Table 2). The most common atopic feature was rhino-conjunctivitis and there were also some cases of asthma and atopic dermatitis. The phenotypic diversity of the patients, from patients with multiple food and environmental sensitizations to patients with no atopic traits or associated respiratory pathology, was noteworthy. We also encountered a number of patients who said their digestive symptoms were worse during respiratory symptom aggravation periods due to pollen exposure.

Table 2. *Food sensitization objectified in each patient included in the protocol. We show which foods were clinically relevant after follow up.*

Patient	Food triggers	No relevant
1	Egg, nuts, legumes/rice, gluten, fruits, tomato/solanaceae	
2	Egg, milk, nuts, legumes/rice, gluten	
3	Nuts, legumes/rice, fish, gluten	
4	Egg, milk, nuts, legumes/rice	
5	Gluten, fruits	
6	Nuts, legumes/rice, gluten, anisakis	Legumes/rice (cooked)
7	Milk, gluten, fruits, meats	
8	Nuts, legumes/rice, gluten, fruits	
9	Panallergens (LTP/profilin)	
10	Seafood, fish	
11	Milk, fruits	
12	Nuts, legumes/rice, gluten, fruits	
13	Milk, fish, fruits, anisakis	
14	Egg, milk, nuts, legumes/rice, gluten, fruits	Egg, milk
15	Egg, milk, nuts, gluten	
16	Egg, milg, nuts, legumes/rice, gluten	
17	Nuts, legumes/rice, gluten, fruits, panallergens (LTP/profilin)	
18	Fruits, panallergens (LTP/profilin)	
19	Nuts, gluten, panallergens (LTP/profilin)	Gluten
20	Nuts, legumes/rice, gluten, fruits	
21	Milk, gluten	
22	Egg, milk, nuts, gluten	Milk
23	Gluten	
24	Seafood	
25	Gluten	

Analytical Values

At baseline, all our patients presented with high ECP levels compared with the normal accepted standard [16], with average levels of 32.57 µg/mL±18.74. We first analysed the changes in the ECP levels in the 29 patients initially included in the study without correction for possible diet transgressions or blood samples taken during a seasonal period (patients with empirical diets, no follow-up or associated diseases such as eosinophilic colitis or ulcerative colitis were discarded), and we observed a statistically non-significant reduction in the ECP levels to 29.81 µg/mL ±8.65 (p=0.25). In this group of patients, we observed an increase in the ECP level after the reintroduction of food triggers to 38.84 µg/mL±22.75, which was significantly different from the previous ECP level (p=0.036). We measured a basal peripheral blood eosinophil count of 400±176.38. The eosinophil count after following the diets was 294.74±171.51. An increase after reintroduction of food was observed, and the eosinophil count reached 410±240.12. The variation was striking but not statistically significant (p =0.134).

However, when we included only the 25 patients who followed the protocols regarding dietary transgressions and blood sampling without respiratory symptoms, we observed a pre-diet ECP mean level of 38.28 µg/mL±23.05 and a post-diet ECP mean level of 23.13 µg/mL±12.65, and these two values were significantly different (p<0.001) (Figure 1). In this group of patients, a striking increase in the ECP level to 32.91 µg/mL±15.74 was observed after reintroducing food triggers, but this increase did not reach the level of statistical significance (p=0.064). The baseline peripheral eosinophilia level prior to beginning the diets was 381.82±181.62. A decrease to 281.82±181.62 was observed after the introduction of the specific diets, and a subsequent increase to 340.91±264.86 was observed after reintroducing the triggers; however, these variations were statistically non-significant (p=0.13) (Figure 2).

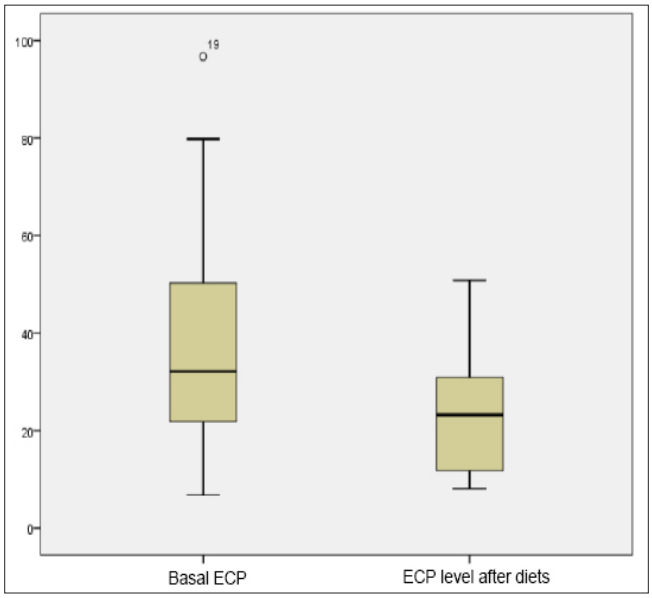

Fig 1. *Significant differences between the baseline ECP levels (38.28± 23.05) and the post-diet ECP levels (23.13± 12.65) (p<0.001).*

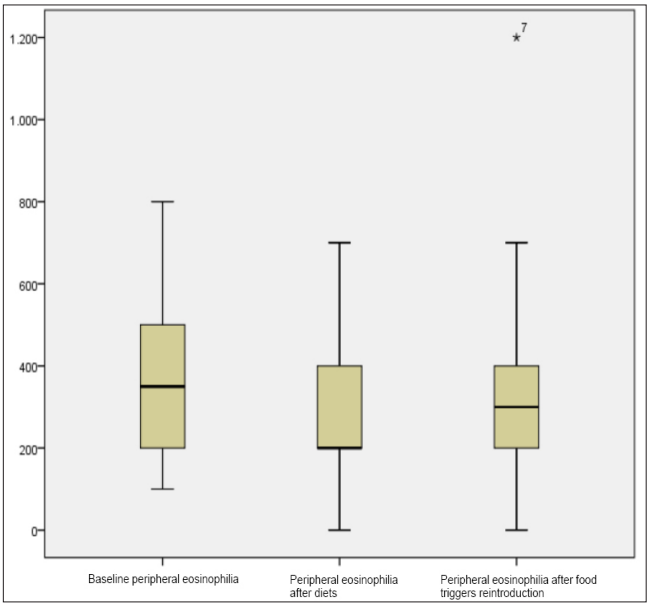

Fig 2. *The baseline peripheral eosinophilia level prior to the specific diets was 381.82 ± 181.62. A decrease to 281.82 ± 181.62 was observed post-specific diets (p=0.13) and a subsequent increase to 340.91 ± 264.86 was observed after reintroducing triggers.*

When we performed a detailed analysis by group, we observed that in the group that did not comply with the protocol eliminating trigger foods (n = 8), the baseline ECP level was 34.36 µg/mL±15.89, and the serial ECP level was 60.88 µg/mL±52.37. There was also no observable change in the level of eosinophilia (pre-diet level of 414.29±157.36 and post-diet level of 414.29± 86.44). In the group that did not comply with the protocol of avoiding blood collection during the period of respiratory symptom exacerbation (n = 5), we observed a baseline ECP level of 24.02 µg/mL±17.40 and a serial ECP level of 39.72 µg/mL±19.93. Finally, in the small group (n = 3) of patients without observed food allergies who opted for empirical diets, a baseline ECP level of 19.60 µg/mL±17.65 and a serial ECP level of 17.40 µg/mL±14.07 were observed, and the peripheral eosinophilia level decreased from 400±200 to 233.33±57.73.

Clinical Response

Twenty-four of the 37 patients (64.86%) showed optimal responses to their specific diets and remained asymptomatic without pharmacological treatment. This response was assessed using the adult eosinophilic oesophagitis quality of life questionnaire (EoO-QOL-A) [17, 18]. However, the results are more striking if we consider the patients who strictly complied with the diets and study protocol, as 96% of them improved significantly (24 of 25). In the long-term follow-up, three of our patients with improvement by following their specific diets chose not to maintain the diets and preferred disease control via drug intervention (PPIs). Of the 3 patients who following empirical diets [19], all showed clinical improvement. However, 2 of these patients opted for PPI therapy with a good response because they were unable to maintain their diets strictly. Of the 25 patients who strictly complied with the protocol, only one did not show improvement by avoiding the identified trigger food (gluten), and disease in this patient was ultimately controlled with omeprazole. Five of the patients (20%) who responded to their specific diets, presented resolution of the eosinophilic inflammation and/or mucosal banding observed in the first endoscopic study. In the rest of the patients, endoscopic studies were not carried out after the diets. Two responding patients required symptomatic treatment during the seasonal period and followed their specific diets for the rest of the year.

Discussion

We present 25 patients diagnosed with EoE in which skin prick allergy tests and the determination of specific IgE levels in all patients and microarrays in some patients, as well as the detection of inflammatory mediators such as ECP or peripheral eosinophilia, were useful to identify relevant food triggers and aeroallergen and panallergen sensitizations. The results of this study indicated that specific diets were effective in the majority of patients (96%) who strictly complied, allowing these patients to abandon or reduce their pharmacological treatment. We were able to determine statistical significance in relation to the use of ECP as an inflammatory marker to determine the influence of the withdrawal and reintroduction of food allergens. The variations in peripheral eosinophilia were striking but not statistically significant in our study. Not observing statistical significance in the variations of peripheral eosinophilia was somewhat expected. We consider that the ECP is more specific and that eosinophils in peripheral blood can guide us in the follow-up, but with less utility. This result agrees with previous observations [20].

Our study offers information on the aeroallergen and food sensitization profile, ECP baseline levels, total IgE levels and peripheral eosinophilia of a series of 37 patients, regardless of whether these patients could be included in the long-term follow-up protocol assessing the withdrawal or reintroduction of food allergens. The patients who were not included in the follow-up were those without food allergies (indicating empirical diets or pharmacological treatment), those who committed food transgressions, those whose mediators were measured during periods of respiratory symptom exacerbation and those with associated diseases such as inflammatory intestinal diseases, eosinophilic colitis or active intestinal or respiratory infection. Of course, it was also not possible to include the patients who did not attend the pertinent follow-up consultation.

EoE is a complex entity characterized by a variety of phenotypes. It predominantly affects men between 30 and 40 years old, and it is generally diagnosed at least three years after the onset of symptoms involving sensitization to foods and environmental aeroallergens [21]. However, it is becoming increasingly apparent that EoE may be an underdiagnosed entity with a late diagnosis. This delay highlights the importance of actively searching for patients with compatible

symptoms, as early diagnosis is fundamental to avoid the development of complications, such as impaction of the alimentary bolus. In our experience, doctors should suspect this condition if patients report episodes of choking or if "atypical" adult food sensitizations such as allergies to milk, eggs or gluten are detected. The patient should then be referred to a digestive medicine specialist for endoscopy and biopsy to confirm the suspected diagnosis. In fact, in our practice, we have gone from studying patients referred after a consultation with a gastroenterologist to the inverse process, where we have detected patients with allergic sensitization profiles and baseline ECP levels compatible with possible EoE, referring these patients to digestive medicine specialists and confirming the EoE diagnosis later. Thinking actively about this disease is essential to ensuring that it does not remain underdiagnosed.

Recent studies [22] have further described the therapeutic management of patients with EoE. It is noteworthy that clinical and histological improvements can be achieved in 50.5% and 60.8% of patients, respectively, using PPIs alone. Treatment with topical steroids (particularly fluticasone and budesonide) is also efficient. Although treatment with PPIs or topical corticosteroids allows for good disease control in patients, life-long dependency on this type of treatment is not desirable. Establishing a diet that allows patients to control their condition long term without depending on chronic treatment is preferable. As previously discussed, the phenotypic variability of EoE makes it impossible to formulate simple treatment rules. A profile must be established for each patient with esophagitis, and the treatment regimen must be adapted for each patient. Based on our experience, specific diets were the dietary regimen most widely accepted by patients, as specific diets are easier to follow than elemental (infeasible in adults) and 6-food empirical diets. Unfortunately, this approach is not always possible.

In our case, the high prevalence of food allergen detection and the possibility of initiating specific diets with a high degree of efficacy probably correspond to the systematic implementation of extended batteries in all patients with a total of (at least) 85 items in the skin prick test and 32 determinations of specific IgE levels as well as microarrays to confirm sensitizations to panallergens such as profilin or LTP. The good response observed after recommending the diets is explained because we gave our patients indications about which food groups to avoid and how they should eat certain foods with a high content of profilin or other panallergens (for example, peeling, freezing or cooking them)

In our opinion, the response to allergen exposure as well as the chronic evolution of inflammation and fibrosis in patients with EoE are enormously similar to the response and evolution observed in patients with asthma and allergic sensitization to environmental aeroallergens. We must remember that patients with asthma have chronic inflammation and that the mechanism of sensitization to aeroallergens is IgE mediated. Anaphylaxis is not characteristic of patients with asthma due to aeroallergen exposure in the same way that it is not characteristic of patients with EoE and allergic sensitization to food triggers. Another very important similarity is the variety of asthma phenotypes with allergic patients who benefit from allergens avoidance and immunotherapy approaches and other ones who have no detected environmental allergies depending on pharmacological treatment as inhaled corticosteroids.

We think that the "asthma" model and mixed mechanisms observed in processes such as food protein contact dermatitis [23,24] explain EoE patient symptoms and evolution very well.

Conclusions

Given the results obtained in our study and the studies described, we think that the recommendation to not perform allergy tests on patients with EoE is not correct. We believe that this recommendation is not consistent considering that empirical diets of 4 or 6 foods, which are widely accepted, are based on the detection of food allergens through allergy tests such as the skin prick test and specific IgE level measurements. We think that there are EoE phenotypes with an important allergic background in which allergy tests such as the skin prick test or specific IgE level measurements, as well as the detection of inflammatory mediators such as ECP, are very useful for trigger detection and follow-up. Recent publications relate the ECP decrease with the inflammation improvement observed in the esophageal mucosa in EoE patients [25]. It is essential to identify the patient phenotype [26] under study to offer the best options in terms of treatment, recommendations and follow-up. We will continue to expand our database with a larger series of patients. It

is essential to better understand the direct or indirect food allergen detection field to recommend diets that should be reliable and feasible for our patients.

Abbreviations

EoE: Eosinophilic oesophagitis; ECP: Eosinophil cationic protein; PPI: Proton pump inhibitor.

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Ethics Approval and Consent to Participate

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

Author's Contribution

JDW conceived the study and drafted the manuscript. ZFL performed the statistical analysis. VJC, VAT, RRP, IOT, MSC and TCC helped to draft the manuscript and participated in the study design. All authors read and approved the final manuscript.

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