Four-food group elimination diet for adult eosinophilic esophagitis: A prospective multicenter study

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Background: Eosinophilic esophagitis (EoE) is an esophageal disorder predominantly triggered by food antigens. A six-food group elimination diet (SFGED) achieves remission in more than 70% of adult patients with EoE. After individual food reintroduction, just 1 or 2 food triggers for EoE can be identified in 65% to 85% of the patients, so some dietary restrictions and endoscopies after food challenge may be unnecessary.

Objective: To evaluate the efficacy of a four-food group elimination diet (FFGED) (dairy products, wheat, egg, and legumes) for adult patients with EoE.

Methods: Prospective multicenter study. All patients were reevaluated after 6 weeks on an FFGED. Response to the FFGED was defined by clinical and histologic (<15 eos/hpf) remission. Responders underwent reintroduction of each individual food over 6 weeks followed by endoscopy and esophageal biopsies. Nonresponders were offered a rescue SFGED.

Results: A total of 52 adult patients were included, of whom 12 patients (23%) had previous failure to topical steroid therapy. Twenty-eight of the 52 patients (54%) achieved clinicopathologic remission on the FFGED and 6 of the 19 (31%) nonresponders to the FFGED were successfully rescued with the SFGED. Twenty-two of 28 responders to the FFGED (78%) finished the individual food reintroduction challenge. Milk was identified as an EoE trigger in 11 patients (50%), egg in 8 (36%), wheat in 7 (31%), and legumes in 4 (18%). All patients had just 1 or 2 food triggers, with milk being the only causative food in 27% of the patients.

Conclusions: An FFGED achieved clinicopathologic remission in 54% of adult patients with EoE. An SFGED was effective in almost a third of FFGED nonresponders, resulting in a combined efficacy of 72% of both strategies. (J Allergy Clin Immunol 2014;■■■:■■■-■■■.)

Key words: *Eosinophilic esophagitis, four-food elimination diet, six-food elimination diet, diet, treatment*

Abbreviations used

DSS: Dysphagia Symptom Score
EoE: Eosinophilic esophagitis
eos/HPF: Eosinophilis per high power field
FFGED: Four-food group elimination diet
PPI: Proton pump inhibitor
SFGED: Six-food group elimination diet

Eosinophilic esophagitis (EoE) has emerged in recent years as a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation, not responsive to a trial of proton pump inhibitor (PPI) therapy.[1] Solid evidence supports the role of dietary antigens in EoE pathogenesis, to be considered as a distinctive form of food allergy.[2] Currently, EoE represents the most common cause of dysphagia and food impaction in adolescents and young adults and its natural history has been proposed as a progression from an inflammatory to a fibrostenotic stricturing disease.[3,4] Subsequently, the 3 main modes of treatment for EoE are dietary therapy, pharmacologic therapy (ie, topical glucocorticoids), and dilation of esophageal strictures.

As for dietary management, an elemental amino acid–based formula diet, thereby eliminating all potential food allergens, constituted the first evidence in 1995 for the causative role of food in EoE[5] and it has been consistently reported as the most effective dietary approach (>90%) for both children and adults.[6] Because this dietary approach is not practical, eliminating specific foods from the diet has also been evaluated: selective elimination diet based on skin testing, combining food skin prick test and atopy patch test, showed promising results in initial reports.[7,8] Unfortunately, these rates have not been replicated neither in children[9-11] nor in adults.[12-14] Furthermore, a recent systematic review showed an overall limited efficacy of 45.5% (95% CI, 35.4% to 55.7%), with high variability among reported results.[6]

An alternative dietary strategy consists of empirically eliminating food allergens most likely to trigger allergies, regardless of allergy testing. In 2006, an empiric six-food group elimination diet (SFGED) containing foods associated most commonly with food allergies and esophageal eosinophilia in US children (cow's milk protein, soy, wheat, eggs, peanuts/tree nuts, and fish/shellfish) exhibited 74% clinical and histologic improvement in pediatric EoE.[15] The efficacy of the SFGED was also replicated in subsequent adult[16,17] and pediatric studies.[18] According to a recent meta-analysis,[6] its combined effectiveness exceeds 72% while it demonstrates an extreme homogeneity regardless of the patient age or geographical area where instituted.

Overall, specific food triggers identified by sequential food reintroduction challenge after a response to an SFGED have been mostly cow's milk, wheat, egg, and soy/legumes.[16,17,19] In

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addition, most of the patients (65% to 85%) responsive to an SFGED have just 1 or 2 causative foods identified after 6 food challenges and endoscopies, so some dietary restrictions and subsequent endoscopies after food challenge may not be necessary.[16,17,19] Therefore, an empiric diet excluding the 4 most common food groups could presumably be nearly as effective as an SFGED and provide several advantages such as limiting unnecessary dietary restrictions and improving patient adherence, shortening the overall time to complete the food reintroduction process and reducing the number of endoscopies. All evidence on empiric diets for EoE comes from unicenter studies,[15-19] so multicenter studies are required for external validation of dietary interventions in EoE.

The goal of the present study was to prospectively examine the effectiveness of an empirical four-food group elimination diet (FFGED) followed by a rescue SFGED to better understand the most common food triggers for EoE and potentially add novel and advantageous dietary interventions for adults with EoE.

METHODS

Patient selection and eligibility

This was a multicenter quasi-experimental study with a removed-treatment design,[20] prospectively conducted at 4 Spanish hospitals between September 2012 and March 2014. Consecutive adolescents and adults older than 14 years with a diagnosis of EoE, defined by consensus guidelines[1] (dysphagia/food impaction and >15 eos/hpf in esophageal biopsies unresponsive to an 8-week trial of PPI therapy), were eligible for enrollment. Patients were recruited from outpatient gastroenterology clinics. Patients with previous failure of corticosteroid therapy were included but should have withdrawn topical steroids at least 12 weeks before initiating the study protocol. Patients with documented failure of any dietary intervention were excluded. Additional exclusion criteria included a previous diagnosis of eosinophilic gastrointestinal disorder, any potential cause for esophageal eosinophilia different from EoE (Barrett's esophagus, achalasia, caustic or radiation esophagitis, inflammatory bowel disease, neoplasm, use of immunosuppressive or immunomodulator therapy), food-associated anaphylaxis, inability to adhere to an elimination diet, or inability to take biopsies because of the presence of esophageal varices or active anticoagulant therapy.

Four-food elimination diet

Given the fact that the methodology for food reintroduction and the identified food triggers were highly comparable between the US study in children[15] and adult data from Spain[17] on SFGED, we finally designed an FFGED excluding cow's milk, wheat, eggs, and legumes. To avoid the maximum cross-reactivity between food allergens,[21] we decided to eliminate all dairy products (either goat's or sheep's milk can cross-react with cow's milk), all gluten-containing grains (cross-reactive with wheat), and all kind of legumes, such as lentil, chickpea, pea, beans, including peanut, which is a leguminous seed (cross-reactive with soy). Over the study period, patients were allowed to eat rice and corn, all kinds of vegetables, meat, fish and seafood, fruits, along with some specific nuts, such as cashew nut, almond, and hazelnut. They could also drink coffee, tea and herbal infusions, rice/almond/hazelnut milk, soft drinks, and alcoholic beverages, although beer or whiskey consumption was not allowed because of gluten content. Gluten-free products were also permitted, provided they did not contain egg, milk, or soy.

Study design

Physical examinations, clinical data record, and baseline endoscopies with esophageal biopsy, at both distal and proximal esophagus, were performed on each of the recruited patients before treatment. Dysphagia was assessed by means of the Dysphagia Symptom Score (DSS), a nonvalidated instrument used in previously published studies of EoE in adults,[16,22] which assigns points for frequency, intensity, duration of symptoms, and presence of lifestyle changes, with a range from 2 to 18, with greater intensity of dysphagia reflected by higher scores. No allergy skin testing was mandatorily performed before the FFGED.

All included patients followed a 6-week FFGED. No registered dietitian or nutrition specialist was involved in the study. A baseline informative meeting was carried out to provide clear instructions to all researchers. Written information, including a thorough list of foods and sample menus allowed and to be avoided, along with instructions to read food labels carefully were provided to patients. A telephone number and e-mail address were also provided to patients in case of further doubts regarding the FFGED. Treatment with oral, nasal, airway, or swallowed steroids was not allowed 8 weeks before the commencement of the study. Aeroallergen sensitization was not treated concomitantly during the study. Patients were asked to avoid contact with allergens known to cause oral allergy syndrome, although there were no additional dietary restrictions. PPI therapy could be taken for gastroesophageal reflux symptoms. In cases of exacerbated rhinitis or asthma during the study period, anti-H1 or inhaled β2-agonists and anticholinergic bronchodilator drugs were allowed.

After the completion of a 6-week FFGED, clinical and endoscopic reevaluation was performed. A decrease of more than 50% of baseline score after therapy was considered as clinical remission. Histologic remission was defined by an eosinophil peak count of less than 15 eos/hpf after FFGED at both distal and proximal esophagus. Responsiveness to the FFGED was considered on histologic remission at both esophageal sites coupled with clinical response. Those patients achieving clinicopathologic remission underwent systematic food reintroduction to identify food triggers, whereas FFGED nonresponders were offered rescue therapy with an SFGED, that is, an FFGED and additional exclusion of all kind of nuts, fish, and seafood. Patients achieving clinicohistologic remission on the SFGED started a similar food reintroduction process.

Food reintroduction

After complete response to either the FFGED or the SFGED, sequential food reintroduction was performed to identify food triggers. Patients were requested to consume each food group every day for a 6-week period, with endoscopic reevaluation after each reintroduced food. Wheat was the first food to be reintroduced in all cases, followed by milk/dairy products. The order of reintroduction for the remaining foods varied according to patient preferences. If peak eosinophil counts were less than 15 eos/hpf after each single-food challenge, this food was considered to be well tolerated and maintained in the diet. In contrast, if inflammation (>15 eos/hpf) recurred, that food was considered an EoE trigger and removed from the diet; in this case, the next food was immediately reintroduced with no washout period. This process was continued until either all 4 or 6 food groups were added back to the diet, accordingly.

Study end points

The primary study end points were clinicohistologic remission after the FFGED as a first-line therapy in patients with EoE and after the SFGED as a rescue therapy. Secondary end points included identifying causative food allergen(s) through the systematic reintroduction of specific foods and examining predictors of response to the FFGED/SFGED.

Endoscopy, esophageal biopsy specimens, and histologic analysis

All esophagogastro-duodenoscopies were performed with either topical pharyngeal anesthesia or propofol-based sedation, according to patient preference, by board-certified gastroenterologists. Using conventional grasping forceps, at least 4 biopsy specimens were taken from both the distal and proximal esophagus. Endoscopic abnormalities suggestive of EoE were recorded following a standardized classification.[23] Mucosal biopsy specimens were fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin for pathologic examination. They were reviewed by senior

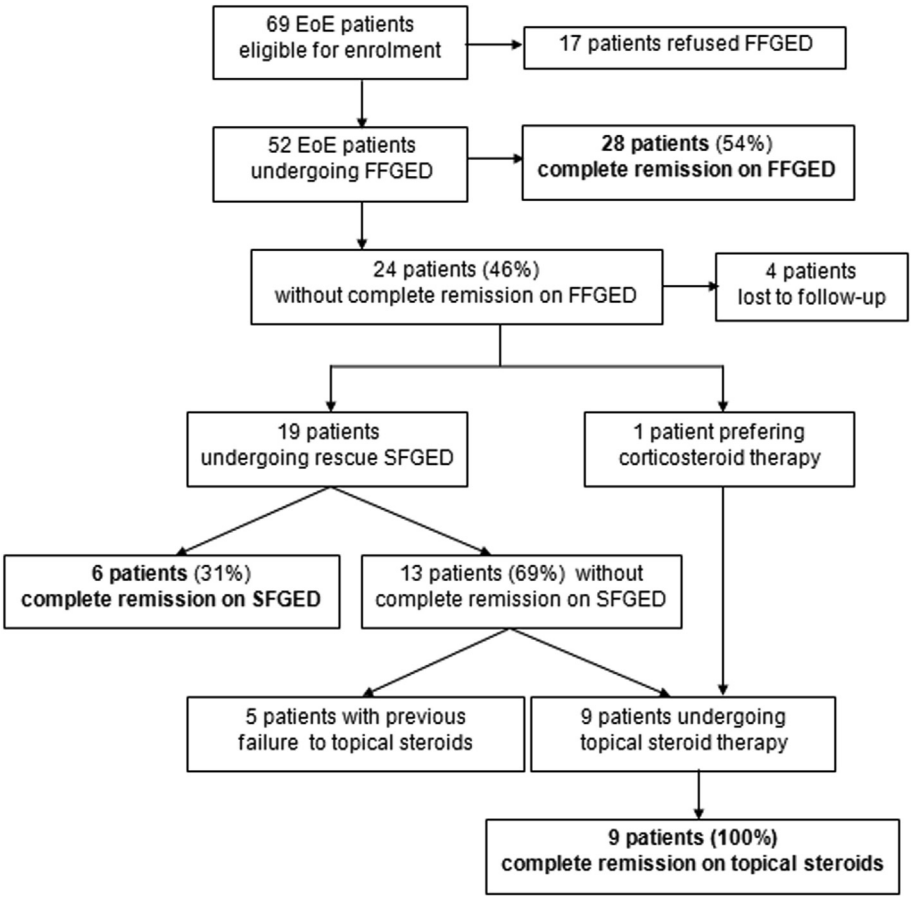

FIG 1. Flowchart of patients during the study.

gastrointestinal pathologists with expertise in EoE in a blinded fashion in each center. One hpf had an area of 0.24 mm^2. The peak count of intraepithelial eos/hpf (×400) was determined in the area of highest density of eosinophils by the most densely populated hpf and esophageal eosinophilia was established on the presence of 15 or more eos/hpf in at least 1 field.[1]

Statistical analysis

The SPSS (version 17.0; SPSS, Inc, Chicago, Ill) statistical analysis package was used. Categorical variables were described with percentages, and continuous variables were described with mean ± SD or median (range) as appropriate. Associations between categorical variables was tested with the χ^2 test (with Fisher correction when necessary), and continuous data were assessed using the 2 sample *t* test or the Mann Whitney *U* test for parametric and nonparametric data, respectively. A signed Wilcoxon rank test was used to assess for a difference in eosinophil counts and symptom scores before and after FFED treatment and after reintroduction of the trigger food.

Univariate analysis was performed to evaluate significant predictive variables for remission on the FFED. The dependent variable was remission on the FFED, and independent variables were age, sex, history of atopy, presence of heartburn, previous failure of topical steroid therapy, diet institution during pollen season (from March to June in Spain), and concomitant PPI therapy during the FFED. A multiple logistic regression analysis was performed using variables with statistical significance on both univariate analysis ($P < .1$) and clinical significance. We used a backward modeling strategy, and the log-likelihood ratio was the statistic used for model comparison. *P* values lower than .05 were considered statistically significant.

Ethics

All patients included gave their consent to participate in the study. This study was approved by the institutional review board in all participating centers.

RESULTS

Baseline characteristics of patients

Over the recruitment period, a total of 69 consecutive adult patients with EoE were eligible for enrollment. Seventeen patients refused the FFGED because of practical difficulties in following the diet and finally 52 patients were included. After an initial trial of the FFGED, 4 patients were lost to follow-up because they all moved out of Spain to search for a job. The flow of patients during the study and the efficacy of dietary interventions are summarized in Fig 1.

Baseline characteristics of patients included in the study are presented in Table I. There were no significant differences between FFGED responders and nonresponders regarding demographic characteristics, symptoms, endoscopic findings, or density of esophageal eosinophilia in distal or proximal esophagus. At baseline, all included patients consumed the 4 food groups at baseline, with the exception of 1 patient who avoided legumes because of previous glottic edema. Eighteen patients (33%) had oral allergy syndrome to nuts (peanut, almond, hazelnut), fruits (peach, kiwi, melon, strawberry, pineapple, watermelon), and vegetables (tomato and celery). All patients fulfilled long-term avoidance of these foods before enrollment.

Efficacy of FFGED

Clinical remission was accomplished in 35 of 52 patients (67%), and the DSS at baseline significantly decreased after the FFGED (9.12 vs 4.30; $P < .001$). Of note, the DSS significantly decreased in both FFGED responders and nonresponders, although to a higher extent in the former group (Fig 2).

TABLE I. Baseline characteristics of patients included in the study

Characteristic	Overall	FFGED responders	FFGED nonresponders	*P* value
No. of patients	52	28	24	
Demographic characteristics, n (%)				
Male/female	33/19 (63/37)	19/9 (67/23)	14/10 (58/42)	.30
Age (y), mean (range)	35 (16-68)	36 (18-68)	34 (16-64)	.64
Atopy	45 (86)	27 (96)	18 (75)	.13
Rhinoconjunctivitis	28 (53)	17 (61)	11 (46)	.12
Asthma	22 (42)	13 (46)	10 (42)	.27
Food allergy before EoE	6 (11)	3 (11)	3 (12)	.62
Symptoms, n (%)				
DSS, mean	9.12	9.05	9.79	.37
Dysphagia	49 (94)	26 (93)	23 (96)	.73
Food impaction	38 (73)	20 (71)	18 (75)	.56
Heartburn	22 (42)	14 (50)	8 (33)	.11
Endoscopic findings, n (%)				
Normal endoscopy	3 (5)	2 (7)	1 (4)	.53
Endoscopic pattern of EoE	49 (94)	26 (93)	23 (96)	.71
Rings	33 (63)	18 (64)	15 (62)	.62
Longitudinal furrows	41 (79)	22 (78)	19 (79)	.7
Whitish exudates	26 (50)	12 (43)	14 (58)	.27
Edema	47 (87)	25 (89)	20 (83)	.75
Narrow caliber esophagus	7 (13)	3 (11)	4 (16)	.69
Feline esophagus	8 (15)	3 (11)	5 (20)	.3
Stricture	2 (4)	1 (3)	1 (4)	.8
Crepe paper esophagus	2 (4)	1 (3)	1 (4)	.8
Esophageal eosinophilia, mean (range)				
Distal esophagus, eos/hpf	55 (10-150)	50 (10-150)	60 (20-130)	.29
Proximal esophagus, eos/hpf	55 (15-135)	50 (15-120)	60 (20-135)	.27

Qualitative variables are expressed as absolute values and proportions. Continuous variables are expressed as mean (range).

Regarding histologic response, 28 of 52 patients (54%) achieved histologic remission after FFGED therapy (Fig 3). The FFGED resulted in a significant decline in esophageal eosinophilia at distal esophagus (55.10 eos/hpf vs 24.04 eos/hpf; $P < .001$) and at proximal esophagus (56.59 eos/hpf vs 23.68 eos/hpf; $P < .001$). In those achieving remission, mean esophageal eosinophilia decreased from 50.36 eos/hpf to 2.56 eos/hpf at distal esophagus ($P < .001$) and from 50.68 eos/hpf to 3.20 eos/hpf at proximal esophagus ($P < .001$). The endoscopic and histologic outcome after the FFGED is presented in Table E1 in this article's Online Repository at www.jacionline.org.

Results of food challenge by sequential reintroduction in FFGED responders

Twenty-two of 28 FFGED responders (78%) completed the food reintroduction process. The results are summarized in Table II. Milk was identified as an EoE trigger in 11 patients (50%), egg in 8 (36%), wheat in 7 (31%), and legumes in 4 (18%). A single offending food group was identified in 10 patients (45%), and 2 offending food groups were identified in 9 patients (45%). No patient was found to have 3 or more offending food groups after food challenge. Interestingly, 2 patients (9%) completed the 4-food group challenge without histopathologic recurrence.

Influence of concurrent PPI therapy and pollen season on the efficacy of FFGED

Similarly to demographic, clinical, endoscopic, and histologic features, neither concurrent PPI therapy (54.9% vs 66.7%; $P = .30$) nor coincidence of pollen season (56% vs 45%; $P = .61$) during diet institution was different between responders and nonresponders to the FFGED. As such, no multivariate analysis could be performed to detect predictive factor of responsiveness to the FFGED.

Efficacy of rescue SFGED

Among 24 patients unresponsive to the FFGED, 19 patients (79%) underwent rescue SFGED (Fig 1). Histologic remission was achieved in 6 of the 19 (31%) patients. All these 6 patients had previously achieved clinical remission of the FFGED, despite the absence of histologic remission, and remained asymptomatic on the SFGED.

Intercenter variability in the efficacy of dietary interventions (FFGED and SFGED)

The FFGED was effective in 54% (28/52) of the patients and the SFGED in almost a third of FFGED nonresponders (6/19), resulting in a combined efficacy rate of 72% (34/47) of the FFGED and the SFGED. One of the participating centers (Valladolid) showed a notably low efficacy for the FFGED (30%), but, on the contrary, exhibited a high efficacy for the SFGED (50%). These results are presented in Table III. Interestingly, both dietary interventions led to clinicopathologic remission in 7 of 12 (58%) patients with previous failure of topical steroids.

Efficacy of topical steroid therapy in patients unresponsive to either FFGED/SFGED

Finally, 14 patients did not respond to or rejected dietary interventions. Five of them had had previous topical steroid

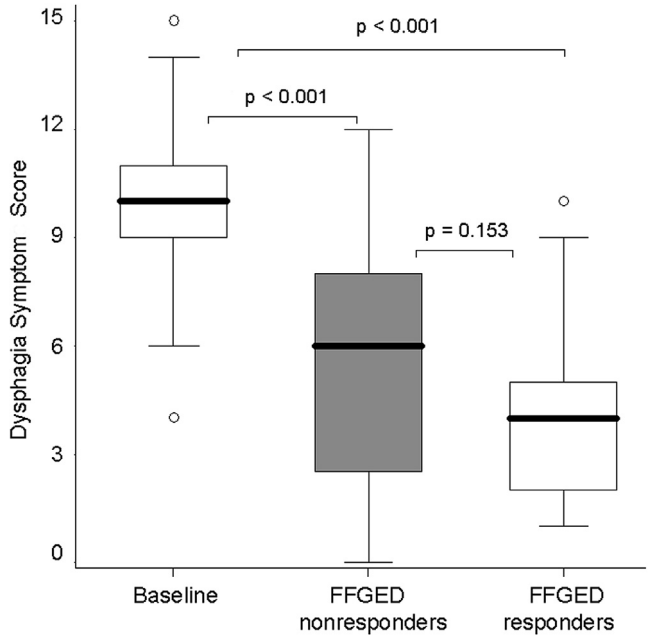

FIG 2. Clinical response after the FFGED, measured by means of the DSS.

failure, whereas the remaining 9 were treated with swallowed fluticasone propionate, nasal drops, 400 μg bid for 6 weeks. All these 9 patients achieved histologic remission on topical steroids (Fig 1).

DISCUSSION

In this prospective multicenter study, we have proven empiric FFGED to be an effective and reproductible dietary therapy for adult patients with EoE, capable of achieving clinicopathologic remission in more than half of the patients. In addition, a rescue SFGED achieved disease remission in almost a third of the patients who had failed the FFGED, overall providing a 72% remission rate, which exactly coincides with previously reported effectiveness for empiric SFGED-based approaches in a recent meta-analysis.[6] However, the new combined-multistage approach of dietary treatment of EoE that we developed here can lead to clear advantages for both patients and the burden of EoE over health care systems. With FFGED as a first-line dietary intervention for EoE, 3 of every 4 responders to the SFGED achieved complete remission of the disease without avoiding fish/shellfish and nuts, with a 12-week shortening of the food reintroduction process and, more importantly, eliminating 2 endoscopic procedures after fish/shellfish and nuts challenge. Compared with the SFGED, the FFGED provides a faster, cheaper, and less inconvenient drug-free effective initial therapy for most adult patients with EoE. Of note, a response to an FFGED/SFGED was also documented in 58% of the patients with previous failure to swallowed topical steroids. Finally, skin testing for food allergy was not necessary and a dietitian was not involved in the study.

The effectiveness of our FFGED of 54% is in agreement with preliminary results from Chicago, where 13 adult and 15 pediatric patients with EoE followed a milk-, wheat-, egg-, and soy-free diet. Histologic remission (peak eos count <10 eos/hpf) was documented in 46% and 60% of adult and pediatric patients, respectively.[24] Our series represents one of the largest in adults after the previous Spanish study[17] and, of note, reintroduction food challenge was completed in the bulk of FFGED responders. Concordances in effectiveness rates and the type of involved foods for empiric SFGED and FFGED elimination diets among American and European studies may be due to the many similarities of staple diets in both regions, which share a common cultural and dietary background. In the previous Spanish study on SFGED,[17] a third of the patients were found to have a single food trigger, another third 2 food triggers, and the remaining third 3 or more food triggers. In contrast, a single offending food was demonstrated in 72%[19] and 85%[16] of pediatric and adult US patients with EoE undergoing an SFGED, respectively. A clear explanation for differences in the number of specific food triggers, identified by means of food reintroduction challenge, between United States and Spain is unknown. Differences in dietary consumption habits and sensitization patterns between both geographical regions may explain this fact. Regardless of these differences, the FFGED may be a more reasonable initial empiric approach to accurately screen patients with EoE with just 1 or 2 causative food groups in any geographical area.

Our findings reconfirm milk as the major EoE-related food in Spanish adult patients,[17] after identifying EoE recrudescence after milk challenge in 50% of responder cases. A milk elimination diet has been proposed as a simple therapeutic intervention for children with EoE, after showing significant histologic remission and improvement in symptoms in 65% of the cases retrospectively recruited at a pediatric facility.[25] Notwithstanding the fact that this unexpected high efficacy should be replicated in further research, we can infer that a milk-free diet would have achieved EoE remission in just 6 of 22 (27%) patients in our prospective adult series. In any case, the high involvement of milk as the most common food trigger for EoE contrasts with the very poor precision of milk skin testing when its results are negative[26]: Its negative predicted value for remission did not better that 40% according to several studies.[18,27]

The overall efficacy in terms of histologic remission of our FFGED in adults is quite similar to that recently reported in children for a diet targeted by skin allergy test/atopy patch test results.[18,27] However, inconsistence in testing precision and technique across centers has reduced the overall efficacy of skin allergy testing to 45.5% of cases (95% CI, 35.4% to 55.7%), according to a recent meta-analysis, which also showed a significantly lower efficacy for adult patients than for children.[6] In fact, the low negative predictive values of foods most commonly reintroduced in single-food challenges have led to some authors to consider that the development of dietary advancement plans for patients with EoE cannot be solely based on skin test results.[18]

Our study has the strength of being the first prospective research on dietary therapy in EoE with a multicenter fashion; patients were recruited at 4 Spanish hospitals located in different regions, obtaining similar results and reinforcing the external validity of our results. Furthermore, we evaluated for the first time the seasonal impact on EoE response to diet and recrudescence after food challenge. A seasonal variation in EoE diagnosis and symptoms had been reported, with both increasing during the months with higher environmental pollen concentrations.[28-30] We could not demonstrate an association between pollen season and the outcome of FFGED or food challenge results, providing us with additional evidence of a strong association of adult EoE with exposition to food allergens instead of airborne ones. Relevantly, EoE recurrence after food challenge was not documented

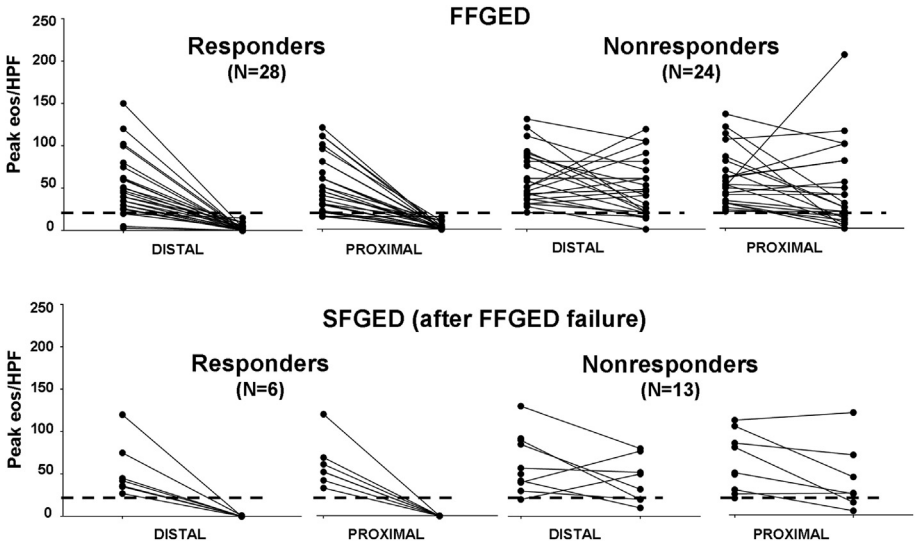

FIG 3. Histologic response after the FFGED (28/52, 54%) and after rescue SFGED (6/19, 31%). The *dotted lines* indicate the 15 eos/hpf threshold.

TABLE II. Food triggers identified by sequential food challenge (n = 22) after response to the FFGED

A single causative food group	10/22	45%
Milk	6/22	27%
Wheat	3/22	13%
Egg	1/22	4%
Two causative food groups	10/22	45%
Milk and egg	2/22	9%
Milk and legumes	2/22	9%
Milk and wheat	1/22	4%
Wheat and egg	3/22	13%
Egg and legumes	2/22	9%
Three or more causative food groups	0	0
No causative food group	2/22	9%

TABLE III. Intercenter variability regarding the efficacy of FFGED and SFGED

Participating centers	FFGED	SFGED after FFGED failure	FFGED + SFGED
Tomelloso	14/20 (70%)	0/6	14/20 (70%)
Caceres	7/14 (50%)	3/6 (50%)	10/13 (78%)
Valladolid	3/10 (30%)	3/6 (50%)	6/9 (66%)
Ciudad Real	4/8 (50%)	0/1	4/5 (80%)
Overall	28/52 (54%)	6/19 (31%)	34/47 (72%)

in 2 of our FFGED responders, who maintained disease remission after resuming a normal diet. The significance of this fact, which has also been described in 4 of the 36 children responsive to an SFGED who underwent sequential food reintroduction,[19] remains unknown. Sampling error in esophageal biopsies, misdiagnosed PPI-responsive esophageal eosinophilia, or influence of pollen season may be potential explanations. Although it is tempting to speculate that temporary food avoidance may induce tolerance in some EoE cases, recent data in pediatric EoE have shown that the disease universally reappears after food reintroduction in every child who had been in remission for a period of up to 4 years.[19]

The present study has several limitations, such as the limited number of recruited patients, the lack of a control group, and the absence of previous allergy workout skin allergy testing in our patients. However, we do not believe that these drawbacks may have an impact on our results because the overall effectiveness rate of 72% for FFGED plus rescue SFGED was almost identical to that reported for SFGED by the first meta-analysis on dietary interventions for EoE.[6] Our quasi-experimental design is an appropriate approach to infer causal relationships. Had we performed a randomized controlled trial, the utility and effectiveness of dietary interventions would not have been properly assessed because many aspects may affect the allocation of patients, masking patients and researchers regarding diet is complicated, and the comparison group (eg, a regular diet) will imply ethical concerns. The DSS is a nonvalidated test to assess symptoms in EoE, and it likely explains little correlation between complete clinical and histologic response, as shown previously by other authors.[16] Our FFGED does not exactly eliminate 4 single foods but 4 food groups. Moreover, foods conditioning the oral allergy syndrome (exclusively fruits and nuts) had been previously excluded, as done in routine clinical practice, because of the high rate of systemic reactions in the Mediterranean region. However, SFGED does not specifically eliminate 6 single foods, but 3 major food groups (nuts, fish, and shellfish) made up of dozens of single foods. Furthermore, some studies evaluating the effectiveness of SFGED eliminated foods with positive results on skin testing.[16,19] The design of our FFGED was based on dietary peculiarities of the Spanish diet, with a higher consumption of goat's and sheep's milk and all kind of legumes, and our own successful SFGED scheme in a previous article.[17] Even though our results may be more transferable to settings with similar staple diets and food consumption habits, overall results for variants of SFGED are fully concordant between the United States and Spain.[15-17] Finally, dietitian supervision detecting long-term nutritional deficiencies, although unlikely because of the low level of restriction (just 1 or 2 food groups in FFGED responders), was not assessed.

In conclusion, the present study prospectively demonstrated that an FFGED-based simple empiric dietary intervention achieved disease remission in more than half of adult patients with EoE, providing them with the advantage of an easier to follow restrictive diet and needing less endoscopic examinations to identify specific food triggers through sequential food reintroduction. Besides, patients were not referred to an allergist for skin testing and a dietitian was not involved in the study, so this collectively represents multiple advantages for both patients and health care systems. An SFGED remains an effective rescue treatment for a third of those who failed in responding to an FFGED. Our results exhibit as well the reproducibility of dietary interventions in the first multicenter study on empiric diets for EoE. Overall, this multistage empiric dietary approach may be recommended as a successful alternative to simplify the dietary management for patients with EoE.

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Key messages

- **An empiric FFGED led to clinicohistologic remission in 54% of the adult patients with EoE; almost a third of nonresponders to the FFGED could be effectively rescued with an SFGED, resulting in an overall effectiveness of 72%.**
- **Therefore, 3 of every 4 adult patients achieving remission on an SFGED may achieve it on an FFGED, a less restrictive dietary intervention that requires fewer endoscopies and shortens the food reintroduction process.**
- **All FFGED responders were found to have 1 or 2 food triggers after individual food challenge.**
- **This multistage empiric dietary approach may be recommended to simplify dietary management for patients with EoE, with several advantages for patients and health care systems.**
- **The results of this first prospective multicenter trial on empiric elimination diet for EoE underscore the generalizability of dietary interventions for EoE in clinical practice.**

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TABLE E1. Endoscopic and histologic features after the FFGED in both FFGED responders and nonresponders

Feature	FFGED responders	FFGED nonresponders	*P* value
n	28	24	
Endoscopic findings, n (%)			
Rings	17 (60)	15 (62)	.59
Longitudinal furrows	6 (21)	19 (79)	<.001
Whitish exudates	0 (0)	16 (58)	<.001
Edema	13 (46)	19 (79)	.01
Narrow caliber esophagus	3 (11)	4 (16)	.69
Feline esophagus	3 (11)	5 (20)	.3
Stricture	1 (3)	1 (4)	.8
Crepe paper esophagus	0 (0)	0 (0)	
Histologic findings			
Distal esophageal eosinophilia, eos/hpf	2 (0-8)	45 (26-141)	<.001
Proximal esophagel eosinophilia, eos/hpf	3 (0-10)	71 (32-168)	<.001
Eosinophil superficial distribution	3 (11)	20 (83)	<.001
Degranulating eosinophils	2 (7)	19 (79)	<.001
Eosinophil microabscesses	0 (0)	15 (62)	<.001

Qualitative variables are expressed as absolute values and proportions. Continuous variables are expressed as median (range).