Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: A prospective study on the food cause of the disease

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Background: Although empiric exclusion from the diet of the 6 food groups most likely to trigger allergies achieves eosinophilic esophagitis (EoE) remission in children, data on its prolonged efficacy and effects on adults are lacking.

Objective: We sought to evaluate the efficacy of a 6-food elimination diet in inducing and maintaining prolonged remission in patients with adult EoE.

Methods: Sixty-seven consecutive patients with adult EoE were prospectively recruited and treated exclusively with a diet avoiding cereals, milk, eggs, fish/seafood, legumes/peanuts, and soy for 6 weeks. Subsequent challenge was undertaken by sequentially reintroducing all excluded single foods, followed by endoscopy and biopsies, which were developed every 6 weeks in case of response (eosinophil peak count reduction to <15/high-power field [hpf]). A food was considered a trigger for EoE and removed from the diet if pathologic eosinophilic infiltration (≥15 eosinophils/hpf) reappeared. Food-specific serum IgE measurements and skin prick tests were performed before initiating the diet.

Results: Forty-nine (73.1%) patients exhibited significantly reduced eosinophil peak counts (<15 eosinophils/hpf) before sequential single-food reintroduction. A single offending food antigen was identified in 35.71% of patients, 2 food triggers were identified in 30.95%, and 3 or more food triggers were identified in 33.3%. Cow's milk was the most common food antigen (61.9%), followed by wheat (28.6%), eggs (26.2%), and legumes (23.8%). Prior allergy tests showed no concordance with food-reintroduction challenge results. All patients who continued to avoid the offending foods maintained histopathologic and clinical EoE remission for up to 3 years.

Conclusions: An empiric 6-food elimination diet effectively induced remission of active adult EoE, which was maintained for up to 3 years with individually tailored, limited exclusion diets. (J Allergy Clin Immunol 2013;131:797-804.)

Key words: *Eosinophilic esophagitis, 6-food elimination diet, therapy, treatment, food allergy, remission*

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Eosinophilic esophagitis (EoE) has become an increasingly recognized immune/antigen-mediated inflammatory esophageal disorder associated with food allergies.[1] It manifests with chronic or recurrent symptoms of esophageal dysfunction and is determined by the presence of large numbers of intraepithelial eosinophils in esophageal mucosal biopsy specimens.[1] Because T lymphocytes and mast cells are also abundant in the inflammatory infiltrate, a T_H2-type immunologic reaction has been implicated in the pathogenesis of EoE.[2,3]

The prevalence of EoE has increased over the last few decades, so that it now constitutes the most common eosinophilic gastrointestinal disorder,[4] with an estimated prevalence in the United States and Europe of between 55 and 43 affected patients per 100,000 inhabitants.[5-7] In spite of this, the proper management of EoE remains controversial.

The accumulation of eosinophils in the esophagi of patients with EoE seems to be caused by exposure to certain foods[8,9] or inhalant antigens,[10] which explains why it has traditionally been considered immunoallergic in nature and treated with the same topical corticosteroids used for bronchial asthma.[11] Because EoE is frequently associated with alterations in esophageal caliber, endoscopic dilation has also been frequently used in these patients.[12] However, both of these treatment options have a limited effect, necessitating either repeated interventions or long-term maintenance therapy.

In 1995, Kelly et al[13] provided firm evidence for the immunoallergic origin of EoE after effectively resolving eosinophilic inflammation and its derived symptoms in pediatric patients by feeding them exclusively with elemental amino acid–based formula for 8 weeks. These results were subsequently corroborated in

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Abbreviations used
EoE: Eosinophilic esophagitis
hpf: High-power field
IQR: Interquartile range
PPI: Proton-pump inhibitor
SFED: Six-food elimination diet
SPT: Skin prick test

several large pediatric series,[14-17] but the feasibility of this strategy was limited for practical reasons, especially in adult patients. The next approach focused on trying to eliminate specific foods thought to trigger the disease from the diet.[18] This strategy, based on using different allergy tests, such as skin prick tests (SPTs) and atopy patch tests, to detect food allergies in children, was found to be highly effective in one study,[19] but the results could not be widely reproduced, possibly because of the lack of standardization and validation of food patch testing in children and adults.

The third dietary treatment strategy for managing EoE consisted of eliminating the foods most likely to trigger allergies, regardless of individual allergy test results. Thus in a study conducted in the United States in 2006, 6 foods commonly consumed in the North American diet (cow's milk protein, soy, wheat, eggs, peanuts/tree nuts, and fish/shellfish) were empirically excluded from the diet of a cohort of 35 pediatric patients given a diagnosis of EoE.[15] Seventy-four percent of the patients showed clinical improvement and decreased eosinophil infiltrate in the esophagus, a result that was recently corroborated in a retrospective analysis.[17] This so-called 6-food elimination diet (SFED) was recently retrospectively assayed in patients with adult EoE from the same region and found to resolve infiltration in 70% of cases.[20] Sequential reintroduction of each single food followed by repeated upper endoscopies and biopsies led to the identification of the foods responsible for disease recurrence in these patients.[20,21] However, no studies conducted outside of northwestern America have been published regarding the effect of SFED on EoE; moreover, data on the effect of prolonged avoidance of food triggers in the diets of patients with EoE is lacking.

This study aims to analyze the effect of an empiric SFED-like diet in patients with adult EoE for the first time in Europe. It also analyzes the efficacy of identifying specific food antigen triggers through sequential single food–reintroduction challenge and its concordance with IgE-based allergy tests. Finally and most importantly, for the first time, we evaluate the effectiveness of diets individually tailored to avoid foods identified as EoE triggers in maintaining prolonged remission of EoE.

METHODS

Study design and participants

This quasiexperimental study with a removed-treatment design[22] prospectively examined all patients older than 16 years who were consecutively treated for EoE in the Department of Gastroenterology at the Tomelloso General Hospital (Spain) between January 2008 and September 2010. Diagnostic criteria of EoE included the following[1]: (1) infiltration of esophageal epithelium by 15 or more eosinophilic leukocytes per high-power field (hpf) at ×400 magnification light microscopy; (2) absence of significant eosinophilic infiltrate in biopsy specimens obtained in the gastric and duodenal mucosa; (3) exclusion of gastroesophageal reflux as a cause of eosinophilia through an 8-week pretreatment with omeprazole (20 mg/twice a day) in addition to negative endoscopic results for signs of reflux diseases and optional ambulatory 24-hour pH-metry; and (4) exclusion (through clinical history) of drug intake, parasites, causticizations, hematologic neoplasm, or other illnesses that could give rise to esophageal eosinophilia.

Physical examinations and baseline endoscopies with esophageal biopsy were performed on each of the recruited patients before treatment. Esophageal symptoms were assessed structurally by means of a score validated for achalasia[23] and previously used in patients with adult EoE[24] because there is currently no validated score specifically for EoE (see Table E1 in this article's Online Repository at www.jacionline.org). The duration and intensity of the dysphagia events along with the frequency and intensity of pyrosis and regurgitation were recorded at the beginning of the study and before each subsequent endoscopy was carried out. All patients were asked to follow an SFED-like diet for a 6-week period, avoiding consumption of 6 food groups reported to cause food allergies[21,25]: cereals (including wheat, rice, and corn), milk and dairy products, eggs, fish and seafood, legumes and peanuts, and soy. The list was extended to include additional foods (eg, rice and corn) based on the results of a previous pilot study[26]; processed foods containing these 6 foods as ingredients were also excluded from the diet. Different kinds of meats, fruits, and vegetables were permitted in the diet, as were tea, coffee, and soft drinks. Supplements with an amino acid–based formula adapted to oral consumption (Neocate Advance, 100-g sachets, banana & vanilla flavors; SHS International, Liverpool, United Kingdom) were recommended to every patient to complement the diet, especially to substitute milk. Written information about which foods should be avoided and which should be allowed along with instructions to read food labels carefully were provided to patients by board-certified gastroenterologists in our department. A telephone number and e-mail address were also provided to patients in case of further doubts regarding the SFED.

Treatment with oral, nasal, airway, or swallowed steroids was withdrawn from each patient 8 weeks before commencing the study; no recruited patients were following dietary restrictions because of EoE. Proton-pump inhibitors (PPIs) were allowed, if necessary. In cases of exacerbated rhinitis or asthma, anti-H_1 or inhaled β_2-agonists and anticholinergic bronchodilator drugs were allowed during the food reintroduction period.

Endoscopy and biopsy procedure

All endoscopic examinations were carried out during conscious sedation by board-certified gastroenterologists and were performed with a flexible 9-mm-caliber Pentax EG-2770K gastroscope (Pentax of America, Montvale, NJ) with a 2.8-mm work channel. Biopsy specimens were taken with the aid of a standard needle biopsy forceps (Endo Jaw FB-220U; Olympus Medical Systems, Tokyo, Japan) from the upper and lower esophageal thirds, obtaining a minimum of 5 specimens from each location. These were then fixed in 4% formalin and routinely processed for histopathologic analysis.

No specific complications were observed in any patients after the biopsy procedure, despite the high fragility of the esophageal wall described in patients with EoE.

Histologic study

All the digestive mucosal samples fixed in formalin were routinely processed: sections (5 μm thick) were cut from formalin-fixed, paraffin-embedded blocks and then placed on microscope slides and stained with hematoxylin and eosin. The histologic stains were analyzed by a researcher blinded to the patient's biopsy identity. The peak number of eosinophils was counted in the most densely inflamed areas with the aid of Nikon Eclipse 50i (Nikon, Tokyo, Japan) light microscopy in 3 hpfs at ×400 magnification (the hpf area measured was 0.212 mm^2). The mean eosinophil count per hpf was calculated in the epithelial strata by averaging the eosinophil counts in 3 hpfs.

All biopsy specimens were analyzed by a blinded, board-certified pathologist (J.L.Y.-C.) experienced in studying EoE biopsy samples.

Allergy study

Before starting the SFED-like diet, all study subjects were examined in the allergy unit of our hospital, where they underwent SPTs and had their total and food-specific IgE serum levels determined.

Food-specific serum IgE levels were determined from peripheral blood by using the ImmunoCAP test (Pharmacia Diagnostics AB, Uppsala, Sweden), according to the manufacturer's instructions. Values ranged between less than 0.35 (absent or undetectable allergen-specific IgE) and greater than 100 kU/L (very high level of allergen-specific IgE).

SPTs against commercial food extracts (ALK-Abelló, Madrid, Spain) were performed on the forearm with disposable lancets (ALK-Abelló) by pricking through a drop of the extract, which was then absorbed. Each drop was separated from the next by at least 2 cm. Reactions were recorded by measuring the largest diameter of the resulting wheal (in millimeters) at 15 minutes. Histamine (10 mg/mL) and saline solution were used as positive and negative controls, respectively. Results were considered positive if the wheal diameter was at least 3 mm.

Outcome measures

Outcome measures were based on the histopathologic response to individual food reintroduction after following an SFED-like diet for 6 weeks. Peak eosinophil counts were determined in the area with the highest density, independently of where the biopsy specimen was taken or the biopsy examination site.

Complete histologic response was taken to be a peak count of 0 to 5 eosinophils/hpf, whereas a partial response was defined as a peak esophageal count of between 6 and 14 eosinophils at any esophageal level. No response/failure of the SFED-like diet was defined as peak counts of 15 eosinophils/hpf or greater at any biopsy examination site or at any esophageal level.

Seasonal variations with regard to the moment of endoscopic examination and eosinophil counts were not taken into account in this study.

A sustained response was defined as the absence of pathologic eosinophilic infiltration (≥15 eosinophils/hpf) in biopsy specimens taken during endoscopies performed 1, 2, and 3 years after finishing the food-reintroduction protocol in patients who maintained the SFED during that period with concomitant absence of EoE-related symptoms and no need for additional drug therapy for EoE.

Endoscopy, histopathologic evaluation, and sequential food reintroduction

In cases of complete or partial histologic response, patients underwent sequential challenge. This entailed the reintroduction of each food individually with subsequent endoscopic examinations and biopsies repeated after 6 weeks, according to the protocol described above.

Patients were requested to consume each newly reintroduced food every day for a 6-week period. Wheat was the first food to be reintroduced in all cases, followed by milk and dairy products. The order of reintroduction for the remaining foods varied according to previous results and the patient's preferences to normalize the patient's diet as soon as possible. A general scheme of food reintroduction is shown in Fig 1.

If peak eosinophil counts were less than 15 eosinophils/hpf after each single-food challenge, this food was considered to be well tolerated and maintained in the diet. In contrast, if inflammation (≥15 eosinophils/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. When endoscopic findings were uncertain, the tested food was preventively removed until a definitive histopathologic evaluation could be obtained.

Patients with no histopathologic response on the first examination after starting the SFED-like diet were withdrawn from the study and treated with orally administered fluticasone propionate.

Statistical analysis

Data are shown as means ± SDs for eosinophils. The paired *t* test or Wilcoxon signed-rank test was used to compare histologic values before and after treatment.

The diagnostic accuracy of the allergy study was defined as sensitivity and specificity in comparison with the results of the single food–reintroduction challenge (gold standard). Overall accuracy was calculated with the Youden index (Sensitivity + Specificity − 1), with ranges from 0 (nonuseful test) to 1 (perfect test).

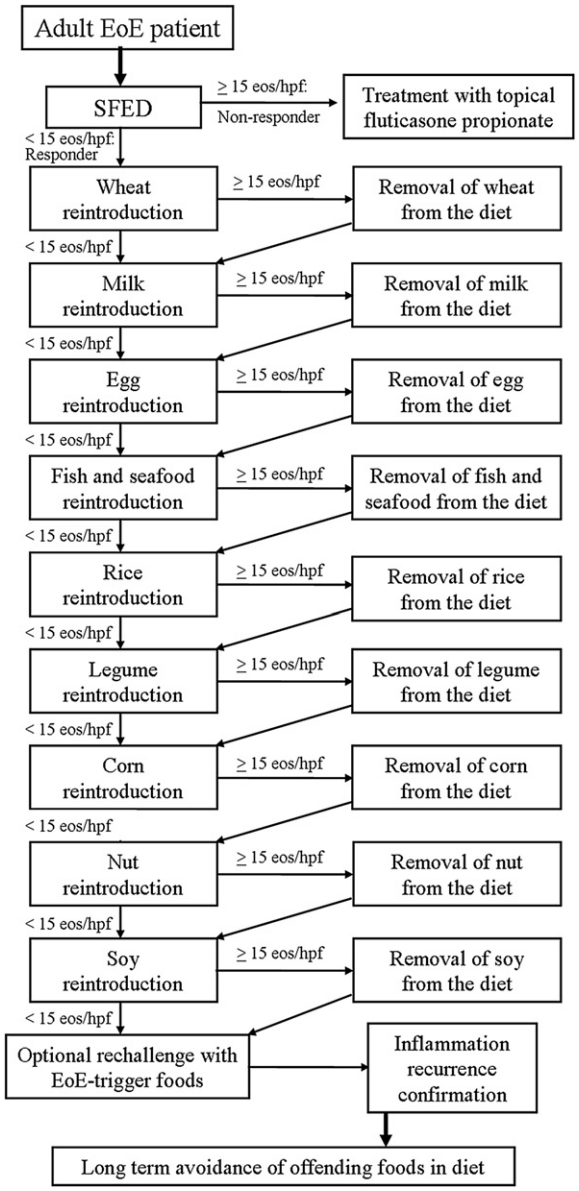

FIG 1. General scheme of the sequential food-reintroduction protocol. Wheat was the first food to be reintroduced in all cases, followed by milk and dairy products. The order of reintroduction of the remaining foods varied according to previous results and the patient's preferences to normalize the patient's diet as soon as possible.

The concordance between the results of the allergy tests and the single-food challenge was measured with the Cohen κ index interpreted in accordance with the criteria set forth by Landis and Koch[27]: A value of approximately 0.5 was considered "moderate," values of greater than 0.81 were considered "almost perfect," and values between 0 and 0.20 were considered "insignificant."

Data are shown as medians with interquartile ranges (IQRs) for scoring clinical symptoms. The Wilcoxon signed-rank test was used to compare values before and after the dietary treatment.

A .05 level of significance was used throughout. Statistical analyses were performed with the aid of PASW 18.0 statistical analysis software (SPSS, Chicago, Ill).

Ethics

The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the institutional review board of our hospital. Informed consent was obtained from all patients before all endoscopic examinations.

RESULTS

We consecutively studied a total of 67 adult patients given a diagnosis of EoE (55 male and 12 female patients) between 17 and 60 years of age (mean, 33.4 years; SD, 11 years). Two patients refused to participate because of practical difficulties in following the diet (Fig 2).

Efficacy of the SFED

In 49 (73.1%) of the 67 treated patients, eosinophilic infiltration decreased significantly from a mean pre-SFED esophageal eosinophil count of 47.9 ± 25.6 eosinophils/hpf to a mean post–SFED-like count of 3.5 ± 3.9 eosinophils/hpf ($P < .001$), with an eosinophilic density of less than 15 eosinophils/hpf in each patient. Among responders, 37 patients achieved a complete histologic response (0-5 eosinophils/hpf), exhibiting a mean post–SFED-like eosinophil count of 0.75 ± 1.29 eosinophils/hpf (rank, 0-3). A partial histologic response (6-14 eosinophils/hpf) was observed in 12 patients, who exhibited an esophageal eosinophil density of 7.78 ± 2.36 eosinophils/hpf (rank, 6-10) after the SFED-like diet (see Table E2 in this article's Online Repository at www.jacionline.org). All 49 responder patients were subsequently challenged with the excluded foods.

The remaining 18 patients showed no significant differences in mean esophageal eosinophil counts before the SFED-like diet (52.5 ± 28.3 eosinophils/hpf) compared with after the SFED-like diet (64.4 ± 24.1 eosinophils/hpf, $P = .539$) and were considered nonresponders (see Table E3 and Fig E1 in this article's Online Repository at www.jacionline.org).

No differences were detected between responders and nonresponders with regard to type or duration of symptoms, endoscopic findings, personal or family atopic background, eosinophilic mucosal density (Table I), or allergy test results (Table II).

Baseline body weight did not significantly change after the SFED; the maximum percentage of weight loss observed was 6% with regard to baseline conditions. No additional losses were documented during the study period.

Results of food challenge by sequential reintroduction

Sequential food reintroduction was carried out in each of the 49 responder patients. A single offending food antigen was identified in 15 (35.71%) patients, 2 offending foods were identified in 13 (30.95%) patients, and 3 or more offending foods were identified in 14 (33.3%) patients. None of the patients completed the 6-food challenge without histopathologic recurrence. Esophageal symptoms recurred in parallel, with histopathologic recurrence after consuming each of the EoE-triggering foods (Fig 3).[23]

The most common food antigen identified as an EoE trigger was cow's milk (in 61.9% of the series), followed by wheat (28.6%), eggs (26.2%), and legumes (23.8%). Other less frequently involved foods are shown in Table III.

Wheat challenge was not developed in 1 patient with a previous diagnosis of celiac disease, whereas milk and nuts, respectively, were not reintroduced in 2 patients with documented anaphylaxis after intake of these foods. In any case these foods were not considered EoE triggers because the affected patients had avoided them in their diets since childhood.

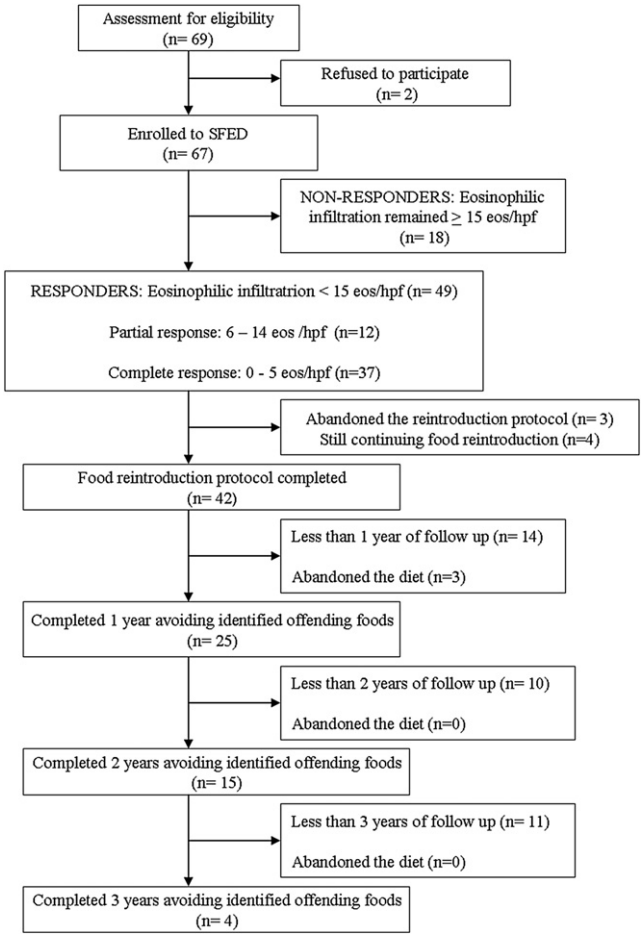

FIG 2. Flow chart with patients included in/completing our SFED and food-reintroduction protocol.

A partial response was observed during the food-reintroduction phase in every patient who exhibited an eosinophil count of greater than 80 eosinophils/hpf for the previously challenged food. Such responses might thus be due to a short recovery time after reintroduction of a highly allergenic food. Complete response was documented at least once in every recruited responder patient.

Relationship between EoE triggers detected by means of sequential food reintroduction and food-specific allergy tests

The degree of concordance between EoE triggers identified through sequential food-reintroduction challenge and allergy testing (IgE serum levels and SPT responses) was also analyzed (Table IV). Compared with the food-reintroduction challenge results, the overall sensitivity of food-specific IgE levels was 32.5%, and the specificity was 77.2%. Similar values were obtained for SPTs (sensitivity, 22.8%; specificity, 78.9%), with both tests showing very low concordance. Discriminatory values, as expressed by using the Youden index, were likewise very low (0.097 for IgE measurements, 0.017 for SPTs, and 0.087 for both combined).

TABLE I. Baseline clinical characteristics of patients with adult EoE included in our study

Characteristic	Patients		*P* value
	Responders	Nonresponders	
Mean age (SD; rank)	32.8 (10.5; 17-57)	34.9 (12.4; 17-60)	.690*
Sex, M/F	39 (79.6%)/10 (20.4%)	16 (88.9%)/2 (11.1%)	.490†
Months of evolution (SD; rank)	54.08 (47.14; 1-204)	87.94 (92.31; 6-300)	.337‡
Symptoms			
Food impaction§	41 (83.7%)	14 (77.8%)	.720†
Dysphagia	33 (67.3%)	15 (83.3%)	.198†
Abdominal pain	10 (20.4%)	4 (22.2%)	1†
Vomiting	5 (10.2%)	1 (5.6%)	1†
Pyrosis	12 (24.5%)	2 (11.1%)	.320†
Weight loss	3 (6.1%)	3 (16.7%)	.331†
Caliber: normal/reduced	36 (73.5%)/13 (26.5%)	11 (61.1%)/7 (38.9%)	.327†
Mucosal appearance			
Normal	4 (8.2%)	2 (11.1%)	.656†
Longitudinal furrows	41 (83.7%)	14 (77.8%)	.720†
Crêpe-paper appearance	19 (38.8%)	5 (27.8%)	.405†
Rings	25 (51%)	9 (50%)	.941†
White plaques	17 (34.7%)	9 (50%)	.254†
Atopic personal history			
Allergic rhinitis	30 (61.2%)	15 (83.3%)	.088†
Drug sensitivity	2 (4.1%)	3 (16.7%)	.116†
Bronchial asthma	22 (44.9%)	10 (55.6%)	.439†
Dermatitis	1 (2%)	0	1†
Food sensitization	16 (32.7%)	6 (33.3%)	.958†
Total serum IgE (U/mL) mean (SD)	528.8 (570.4)	794.1 (654.5)	.087‡
Atopic family history			
Allergic rhinitis	16 (32.7%)	6 (33.3%)	.958†
Drug sensitivity	4 (8.2%)	1 (5.6%)	1†
Bronchial asthma	8 (16.3%)	4 (22.2%)	.720†
Dermatitis	4 (8.2%)	2 (11.1%)	.656†
Food sensitization	6 (12.2%)	1 (5.6%)	.665†
Mean intraepithelial eosinophils before SFED			
Cells/mm^2 (SD)	226.3 (120.9)	247.6 (133.5)	.539‡
Cells/hpf (SD)	47.9 (25.6)	52.5 (28.3)	
Mean intraepithelial eosinophils after SFED			
Cells/mm^2 (SD)	16.5 (18.2)	303.9 (113.5)	<.001‡
Cells/hpf (SD)	3.5 (3.9)	64.4 (24.1)	

F, Female; *M*, male.
*Student *t* test.
†χ^2 Test.
‡Mann-Whitney *U* test.
§Food impaction includes transient esophageal retention of food (self-resolved or resolved after fluid intake) and food bolus impaction requiring endoscopic removal.

Sustained effect in responder patients

One-year follow-up data were available for 25 patients who successfully finished the protocol and continued to avoid the offending foods. Median symptom scores were significantly reduced from 8 (IQR, 6-14) at the baseline situation before the SFED-like diet to 1 (IQR, 0-3) after finishing the food-reintroduction protocol. All of these patients were asymptomatic, with no pathologic eosinophilic esophageal inflammation (<5 eosinophils/hpf) after endoscopy (Fig 3).

Three patients who exhibited a successful response subsequently abandoned the diet because of difficulties in following a wheat/milk/egg-free diet.

Long-term effects and dietary follow-up

Fifteen patients successfully complied with the food trigger avoidance diet for a total of 2 years; of these, 4 were able to maintain it for 3 years of follow-up. All of them remained asymptomatic, with no signs of eosinophilic inflammation (<5 eosinophils/hpf) in their annual endoscopic examinations. No drug treatment for EoE was needed for patients with sustained remission. Considering those patients with the longest follow-up (3 years), wheat was the sole EoE trigger in one of them, cow's milk was the sole trigger in 2 patients, and both foods were triggers in the last patient. Two patients admitted to occasional dietary transgressions, occasionally consuming cheese and ice cream containing milk. No symptoms were reported after such transgressions. Patients with wheat-triggered EoE received support from a celiac disease resource organization.

DISCUSSION

This prospective study corroborates the high efficacy of a modified SFED in achieving histopathologic and clinical remission of EoE, both of which were observed in 73.1% of our patients with adult EoE. These results are comparable with previously reported findings in children[15,17] and also validate recently reported results in adults,[20] all of them from retrospective

TABLE II. Allergy study results (SPTs and specific serum IgE measurements) in adult SFED responders and nonresponders given a diagnosis of EoE

	Positive SPT responses (%)			Specific serum IgE (kU/L)		
	Responders	Nonresponders	*P* value	Responders	Nonresponders	*P* value
Milk	14.7	33.3	.247*	2.77 (3.30)	1.01 (0.47)	.086†
Wheat	29.4	46.7	.242*	3.26 (4.64)	3.06 (2.93)	.690†
Eggs	14.7	40	.069*	1.37 (0.73)	2.33 (2.54)	.935†
Legumes	41.2	53.3	.430*	5.37 (8.14)	9.75 (3.92)	.083†
Rice	14.7	40	.069*	7.03 (10.63)	4.15 (2.86)	.923†
Corn	20.6	40	.178*	9.02 (14.01)	4.98 (5.03)	1†
Seafood	20.6	40	.178*	2.33 (2.33)	5.5 (4.39)	.165†
Nuts	41.2	53.3	.430*	3.07 (1.96)	2.28 (1.51)	.464†
Soy	14.7	33.3	.247*	2.38 (3.31)	3.94 (4.5)	.348†

*χ^2 Test.
†Mann-Whitney *U* test.

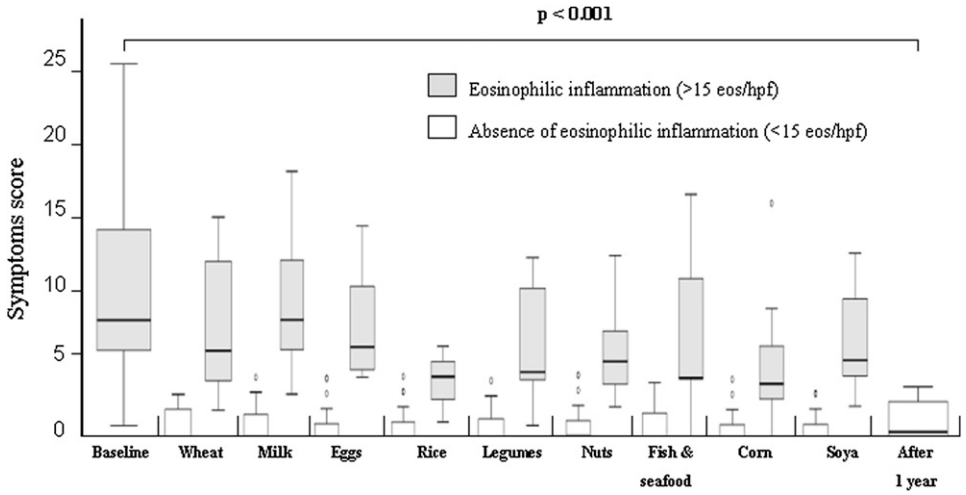

FIG 3. Score of esophageal symptoms in patients with adult EoE: patients at basal conditions, after each food challenge reintroduction, and after 1 year of following a diet without EoE food triggers, as determined by using the method proposed by Zaninotto et al[23] for achalasia. Medians and IQRs are represented in the *boxes*, with *whiskers (vertical lines)* extending to a limit of ±1.5 IQRs.

TABLE III. Food group triggers of EoE in our series of adult patients

Food	No. of patients	Percent
Cereals	29/42	64.28
Wheat	12/42	28.6
Rice	8/42	19
Corn	8/42	19
Milk	26/42	61.9
Legumes/nuts	20/42	37.6
Legumes	10/42	23.8
Nuts	7/42	16.7
Eggs	11/42	26.2
Fish and seafood	8/42	19
Soy	6/42	14.3

Wheat challenge was not tested in a patient with a previous diagnosis of celiac disease; milk and nuts, respectively, were not reintroduced in 2 patients with anaphylaxis after these foods. In any case these foods were not considered EoE triggers because the affected patients had avoided them in their diets since childhood.

observations. We can thus confirm that food antigens are the major triggers in inducing and maintaining eosinophilic esophageal inflammation for patients of all ages, providing additional evidence that pediatric and adult types of EoE constitute a single disease. In addition, this is the first time that follow-up data have been obtained regarding the maintenance of disease remission for up to 3 years in patients with specific EoE food triggers that were identified by means of sequential single-food reintroduction under endoscopic and bioptic control and then continuously excluded from the diet.

Empiric elimination diets involving the exclusion of the 6 food groups most likely to cause food allergies are emerging as a suitable drug-free dietary treatment alternative for both patients with pediatric[15,17] and patients with adult[20] EoE, with comparable efficacy to previously used strategies, especially topical steroids.[1] SFED has also been shown to be a valid alternative to elemental amino acid–based formulas,[17] which, despite their high efficacy in resolving symptoms and normalizing biopsy results in patients with pediatric EoE, have such serious drawbacks that alternative dietary interventions are necessary. Elimination diets based on SPTs and atopy patch tests[18,19,28] have been shown to be efficient in most treated children (77%), but they require the removal from the diet of an average of 5 foods per patient.[17,18] Therefore nearly half the responder patients in these circumstances require

TABLE IV. Concordance (Cohen κ index), specificity, and sensitivity for specific serum IgE measurements, SPTs, and a combination of both in comparison with food challenge results evaluated by recurrence of inflammation in histology

	Specific serum IgE			SPT			Combined serum IgE and/or SPT		
	Sensitivity	Specificity	Concordance	Sensitivity	Specificity	Concordance	Sensitivity	Specificity	Concordance
Wheat	50%	52.4%	0.022	10%	63.6%	−0.271	46.2%	56.5%	0.025
Milk	30%	92.3%	0.190	15%	100%	0.117	30.4%	92.3%	0.182
Rice	28.6%	75%	0.034	28.6%	86.4%	0.165	37.5%	68%	0.049
Eggs	20%	90.9%	0.130	20%	95.2%	0.187	18.2%	91.7%	0.119
Legumes	63.6%	73.3%	0.370	50%	60%	0.098	63.6%	58.8%	0.214
Fish and seafood	0%	90.9%	−0.120	0%	72.7%	−0.273	0%	75%	−0.263
Nuts	12.5%	82.4%	−0.059	50%	50%	0	50%	52.6%	0.022
Corn	42.9%	76.5%	0.193	14.3%	81.3%	−0.051	42.9%	78.9%	0.218
Soy	33.3%	68%	0.011	0%	91.7%	−0.109	33.3%	70.4%	0.029
Overall	32.9%	77.3%	0.083	21.7%	78.2%	−0.015	36.2%	71.2%	0.064

Overall values are calculated as an average of each food.

elemental diet supplements to avoid severe nutritional deficits. We should mention that elemental formulas were also used in our study in some patients as a supplement at the beginning, when the diet was most restrictive, being discontinued after milk, soy, or both were reintroduced and one of them was tolerated.

After eliminating intact food proteins with an SFED, Kagalwalla et al[21] sequentially reintroduced single foods under endoscopic and bioptic monitoring, which allowed the identification of the specific foods that led to disease recurrence. Cow's milk protein was found to be the most frequent EoE trigger (74%), followed by wheat (26%) and eggs (17%); these results have been closely corroborated in our study. A very recently published American study on adult EoE also demonstrated a 70% efficacy of SFED; single-food reintroduction showed that the most frequent trigger food was wheat (60% of cases), followed by milk (50%), soy (10%), and nuts (10%).[20]

One important difference between our work and previously published studies on the use of "classic" SFEDs in EoE is the fact that we restricted more foods from our subjects' diets; in fact, a "modified" SFED that also restricts food eliciting positive SPT and atopy patch test responses has been used with equal effectiveness.[17] Our elimination diet excluded rice and corn along with wheat, all kinds of nuts (including chestnuts, hazelnuts, sunflower seeds, almonds, and pistachios), legumes, and fish. Also, in addition to cow's milk, neither sheep's nor goat's milk–derived products (all of which exhibit cross-reactivity) were allowed in our adult patients' diets. In this way we were able to reproduce the aforementioned good results of pediatric studies and even slightly surpass recent results reported for adults. Differences both in children's and adults' diets[29] and especially in food consumption habits between the northwestern United States and Spain,[30,31] along with specific immunologic patterns in different geographic regions,[32] might help explain why corn, rice, and legumes, which are not included as trigger foods in "classic" American SFEDs, were found to be triggers for EoE in between 23% and 28% of our subjects. The same explanation might also explain why 2 of 3 of our patients with EoE presented more than 1 food trigger, whereas the same was true for only 18% to 28% of patients in the aforementioned American studies.

This finding raises the question of whether empiric exclusion diets should be tailored to each specific region and based on the staple diets and food-sensitization profiles where the patient is being treated. Large, multicenter, transatlantic studies and especially studies conducted in regions with marked dietary differences with regard to westernized diets should help answer these questions.

Our study also found that EoE was triggered by a single food in only 35.7% of adult patients, whereas this is the case in up to 72% of children. This makes adult EoE in our environment more complex because several foods can trigger the disease independently in most patients. It should be noted that elimination diets that exclude multiple food proteins are impractical in the long term and can lead to iatrogenic nutritional deficiencies and behavioral problems.[33] Furthermore, depending on the specific food, maintaining the diet is difficult for many patients. Thus despite the fact that they had successfully responded to the diet and were asymptomatic after following it for months, 3 of our subjects later abandoned it because of the difficulties in following a milk-, wheat-, and egg-free diet. In any case we have demonstrated for the first time that continued avoidance of offending foods from the diets of patients with quiescent EoE can lead to maintained disease remission in terms of symptoms and eosinophilic esophageal inflammation for up to 3 years. Because EoE represents a chronic disorder, the foods proved to trigger it should be avoided indefinitely[1]; however, after demonstrating that a sustained drug-free response is now achievable for most patients with EoE, it is tempting to speculate about the possibility of inducing tolerance with progressive EoE trigger reintroduction after prolonged remission. Further studies are needed to fully explore this possibility.

Our patients were allowed to receive PPI treatment if necessary during the food reintroduction period but not inhaled topical steroids, which would have interfered with our results. Active EoE can associate with esophageal dysmotility and impaired acid clearance, especially in the lower esophagus, leading to secondary gastroesophageal reflux (and occasionally some additional low-grade esophageal eosinophilia in the distal esophagus related to acid exposure).[1] We did not systematically treat all of our patients with PPIs during the whole study protocol because gastroesophageal reflux disease–related symptoms at baseline were not present in some of them, whereas in others symptoms improved after the eosinophilic infiltrate vanished. In any case gastroesophageal reflux disease was excluded as a cause of esophageal eosinophilia in every patient at the moment of enrollment.

It is interesting to note that the various dietary intervention alternatives available to patients with EoE show relatively similar results with regard to efficacy, ranging from 96% to 70%.[13,15-18,20,26,28] We can thus safely assert that in more than 3 of 4 patients with EoE, the disease is triggered and maintained exclusively by food, with a small remainder attributable to airborne allergens, either jointly with food allergies or alone. From retrospective observational studies, we can infer than

most SFED-nonresponder pediatric patients would benefit from receiving elemental formulas,[17] an alternative never assessed in adults because of its impracticality (nonresponder patients in our series received topical steroid-based therapy).

Finally, allergy tests based on demonstrating an IgE-driven hypersensitivity showed limited usefulness in identifying EoE triggers, exhibiting extremely low concordance with the results of food-reintroduction challenges. These findings are in agreement with previous retrospective observations that SPTs do not predict the causal agent in the majority of patients undergoing food reintroduction[20] and have an extremely low negative predictive value.[17] It thus seems that the main pathophysiologic mechanism in patients with EoE might not be IgE-mediated allergies but rather a delayed hypersensitivity reaction against common, regularly consumed foods.[3] Still, studies like ours, based on sequential single food–reintroduction challenges and monitored with repeated endoscopies and biopsies to identify the offending foods, are impractical for general use and have important drawbacks; the establishment of noninvasive or minimally invasive markers to replace the need for multiple endoscopies should thus be a top priority in this field.

Key messages

- **Empiric exclusion of 6 food groups achieved histopathologic (eosinophil peak count, <15 eosinophils/hpf) and symptomatic remission in 73.1% of patients with adult EoE.**
- **Specific food antigen triggers of EoE identified by means of sequential reintroduction challenge were similar to those reported for children, with cow's milk, wheat, and eggs being the most frequently implicated single foods.**
- **Food-specific IgE serum measurements and SPTs were neither sensitive nor specific methods for predicting EoE triggers; indeed, allergy test results showed little concordance with food-reintroduction challenge results.**
- **All patients who continued to avoid the offending foods maintained histopathologic and clinical remission of EoE for up to 3 years after finishing the study protocol, making this a feasible, drug-free maintenance therapy.**

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