CLINICAL—ALIMENTARY TRACT

Elimination Diet Effectively Treats Eosinophilic Esophagitis in Adults; Food Reintroduction Identifies Causative Factors

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This article has an accompanying continuing medical education activity on page e14. Learning Objectives: Upon completion of this assessment, successful learners will be able to understand the evidence supporting the use of dietary therapy in adult eosinophilic esophagitis.

See Covering the Cover synopsis on page 1399; see editorial on page 1409.

BACKGROUND & AIMS: Adults with eosinophilic esophagitis (EoE) typically present with dysphagia and food impaction. A 6-food elimination diet (SFED) is effective in children with EoE. We assessed the effects of the SFED followed by food reintroduction on the histologic response, symptoms, and quality of life in adults with EoE. **METHODS:** At the start of the study, 50 adults with EoE underwent esophagogastroduodenoscopies (EGDs), biopsies, and skin-prick tests for food and aeroallergens. After 6 weeks of SFED, patients underwent repeat EGD and biopsies. Histologic responders, defined by ≤5 eosinophils/high-power field (eos/hpf) (n = 32), underwent systematic reintroduction of foods followed by EGD and biopsies (n = 20). Symptom and quality of life scores were determined before and after SFED. **RESULTS:** Common symptoms of EoE included dysphagia (96%), food impaction (74%), and heartburn (94%). The mean peak eosinophil counts in the proximal esophagus were 34 eos/hpf and 8 eos/hpf, before and after the SFED, and 44 eos/hpf and 13 eos/hpf in the distal esophagus, respectively ($P < .0001$). After the SFED, 64% of patients had peak counts ≤5 eos/hpf and 70% had peak counts of ≤10 eos/hpf. Symptom scores decreased in 94% ($P < .0001$). After food reintroduction, esophageal eosinophil counts returned to pretreatment values ($P < .0001$). Based on reintroduction, the foods most frequently associated with EoE were wheat (60% of cases) and milk (50% of cases). Skin-prick testing predicted only 13% of foods associated with EoE. **CONCLUSIONS: An elimination diet significantly improves symptoms and reduces endoscopic and histopathologic features of EoE in adults. Food reintroduction re-initiated features of EoE in patients, indicating a role for food allergens in its pathogenesis. Foods that activated EoE were identified by systematic reintroduction analysis but not by skin-prick tests.**

Keywords: Stricture; Esophagus; Food Allergy; Inflammation.

Eosinophilic esophagitis (EoE) is one of the most common causes for dysphagia and food impactions in adults.[1–5] Recent consensus guidelines define EoE as a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation.[3,4] Involvement of allergic mechanisms in the pathogenesis of EoE is supported by studies showing esophageal tissue expression of mediators such as IgE, eotaxin-3, interleukin-13, and interleukin-5, and cell mediators including mast cells, dendritic cells, as well as eosinophils.[6] Furthermore, esophageal eosinophilia is induced in a murine model after allergen exposure.[7] The concept of food allergens as the primary trigger of EoE was introduced by Kelly et al[8] in a pediatric cohort with symptoms of gastroesophageal reflux disease and esophageal eosinophilia unresponsive to acid suppression or fundoplication. Both symptoms and eosinophilia resolved

Abbreviations used in this paper: EGD, esophagogastroduodenoscopy; EoE, eosinophilic esophagitis; eos/hpf, eosinophils/high-power field; PPI, proton pump inhibitor; QOL, quality of life; SF-36, Standard Short Form-36; SFED, 6-food elimination diet; SPT, skin prick testing.

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after an elemental formula. This experience has been substantiated in subsequent larger pediatric series.[9,10]

Although elemental diet is effective in children, it can be costly, unpalatable, and necessitate the placement of feeding tubes. A directed elimination diet based on allergy testing showed substantial response rates in pediatric EoE but was ineffective in a small adult series.[11,12] In a retrospective pediatric study, Kagalwalla et al[10,13] reported the effectiveness of an empiric diet, selectively removing the 6 most common food allergens in EoE. In the 6-food elimination diet (SFED), patients avoid ingestion of milk, soy, egg, wheat, peanuts/tree nuts, and shellfish/fish.

There are known phenotypic differences in adult and pediatric EoE patients, which raises the question of whether the disease process is the same in these 2 populations.[14,15] Furthermore, the role of food allergens in EoE and the utility of SFED in the therapy of EoE has not been formally evaluated in adults. The goal of the current study was to prospectively examine the effectiveness of SFED in an adult cohort to better understand the importance of food allergy, thus potentially adding dietary intervention as a novel therapeutic option for adults with EoE.

Materials and Methods

Study Design

This was a prospective clinical trial from 2006 to 2010 performed at a single university medical center. The study was designed to examine the effectiveness of SFED in adults with EoE. All patients underwent an elimination diet for 6 weeks followed by esophagogastroduodenoscopy (EGD) and biopsy. Patients who achieved histologic remission underwent systematic, sequential food reintroduction with follow-up endoscopies and biopsies to identify specific food triggers.

Study End Points

The primary study end point was histologic improvement in esophageal eosinophilia after SFED defined as complete (peak eosinophil count, ≤5 eos/hpf), near complete (≤10 eos/hpf), and partial (>50% reduction of peak eosinophil count). Secondary end points included assessment of symptom response and quality of life (QOL). The study also identified causative agent(s) through the systematic reintroduction of specific foods and examined predictors of response to SFED.

Patient Selection and Eligibility

Adults older than 18 years with a diagnosis of EoE, based on the presence of esophageal symptoms and esophageal biopsy specimens showing 15 or more eosinophils/high-power field (eos/hpf) in the squamous epithelium, were eligible. A baseline endoscopy was performed on all patients with biopsy specimens obtained from the proximal and distal esophagus confirming a diagnosis of EoE (see Endoscopy, Esophageal Biopsy Specimens, and Histologic Analysis section). Before the index endoscopy, patients had completed 8 weeks of twice-daily proton pump inhibitor (PPI) therapy or had a 24-hour pH study showing normal acid exposure. Patients were recruited from an outpatient academic gastroenterology clinic (by N.G. and I.H.) and those who met entry criteria were offered treatment with SFED as an alternative to topical corticosteroids. None of the patients were treated with swallowed or systemic steroids at enrollment or during the study. Patients previously treated with topical corticosteroids had to be off therapy for at least 8 weeks with a repeat endoscopy showing persistent EoE before inclusion in the study. Patients who were on a PPI at the start of the study remained on the medication during the study period. Exclusion criteria included history of Barrett's esophagus, caustic or radiation esophagitis, achalasia or scleroderma, *Helicobacter pylori* infection, inflammatory bowel disease, use of immunosuppressive or immunomodulator therapy (ie, leukotriene inhibitors), food-associated anaphylaxis, or inability to adhere to an elimination diet. Aeroallergens were not treated concomitantly during the study, and no new allergy medication (antihistamines, nasal steroids, and so forth) was instituted.

Allergy Testing

Before the elimination diet, patients underwent skin prick testing (SPT) for food and aeroallergens. Skin testing for aeroallergens included tree, grass, ragweed, mold, house dust mite, cat, dog, and cockroach (ALO; Columbus, OH). Skin testing for food allergens included peanuts, tree nuts, fish, shellfish, egg, wheat, soy, and milk. If patients self-reported additional foods that provoked symptoms, these were tested. Saline and histamine were used as negative and positive controls, respectively. The prick tests were performed using approximately 5000 AU/mL. A positive test was considered a wheal 3 mm greater than the negative control at 20 minutes.

Diet Elimination and Reintroduction

Patients completed 6 weeks of the SFED. If they had additional food allergies based on history or SPT, these foods also were avoided. Before institution of the SFED, patients met with a dietician specifically trained in allergy diet restriction for education and were provided with sample menus and shopping guides. Patients completed a 3-day dietary log within the first 2 weeks of the initiation of the diet, which was reviewed by the dietician to document adherence and possible dietary contamination. If patients self-reported dietary contamination or indiscretion, the SFED period was extended an additional 6 weeks.

After completion of 6 weeks of dietary elimination, an EGD with proximal and distal esophageal biopsy specimens was repeated. Patients achieving the primary end point of histologic improvement underwent systematic food reintroduction to identify potential food triggers. The reintroduction phase consisted of the addition of one food group every 2 weeks. The order of food reintroduction was individualized based on allergy testing or patient preference. An EGD with biopsy specimens was repeated 4 weeks after the reintroduction of 2 food groups. If patients became symptomatic during reintroduction before the 4-week time point, an endoscopy was repeated. Food triggers were implicated if patients had histologic recurrence of EoE. If patients had evidence of recurrence based on the return of esophageal eosinophilia on repeat endoscopy, a 6-week washout period with discontinuation of the implicated food was undertaken. A repeat endoscopy after the washout period was used to confirm resolution of histologic eosinophilia before additional foods were added. This process was continued until all 6 food groups were added back to the diet.

Data Collection

Patients completed a dysphagia symptom score and QOL surveys at the time of enrollment and immediately after completion of the initial 6 weeks of the SFED. The dysphagia symptom score was a nonvalidated instrument used in a previ-

ously published study of EoE in adults.[16] This patient-reported outcome instrument assigned 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 (Appendix A). The Standard Short Form-36 (SF-36) was used to assess QOL both before and after treatment. SF-36 scores were analyzed for physical and mental components as well as for the subcomponents of these scores. The physical component scores were broken down into the following subcomponents: physical function, role physical, bodily pain, and general health. Mental component scores were broken down into the following subcomponents: vitality, social function, role emotion, and mental health. Gender differences and comparisons with normative data were assessed.

Endoscopy, Esophageal Biopsy Specimens, and Histologic Analysis

EGD was performed using an Olympus GIF-XP-H180 videoscope (Olympus America, Inc, Melville, NY). Radial jaw–3 grasp forceps (Boston Scientific, Natick, MA) were used to obtain biopsy specimens. At least 4 biopsy specimens were taken from both the distal and proximal esophagus. The distal esophagus was defined as 5 cm above the squamocolumnar junction, and the proximal esophagus was defined as 15 to 20 cm above the squamocolumnar junction. All biopsy specimens were reviewed by a single gastrointestinal pathologist (G.-Y.Y.) who was blinded to the patient's treatment status, and the specimen was evaluated for peak density of eosinophils per high-power field (40×; 0.1256 mm^2). At least 5 high-power fields were evaluated for each biopsy in the area most densely populated with eosinophils. Tissue specimens from the index and post-treatment endoscopy were stained for ki-67, a marker of cell proliferation and epithelial hyperplasia, which has been shown to be increased in both children and adults with EoE.[17,18] Immunohistochemical staining was performed according to the protocol of the avidin-biotin-peroxidase method (Appendix B).

Data Analysis and Statistics

The primary analysis compared the peak eosinophil counts before and after SFED. Each patient served as their own control. A signed Wilcoxon rank test was used to assess for a difference in eosinophil counts and symptom scores before and after treatment and after reintroduction of the trigger food. Statistical significance was determined by a P value less than .05. Effect sizes were used as a supplement to standard statistical estimates of significance to provide a more complete and clinically relevant picture of health status change[19] (Appendix C). Univariate logistic regression models were fit to determine predictability of complete response. Wald P values for odds ratios and 95% confidence intervals are presented. Predictors of response that were tested included sex, age, history of atopy, history of food impaction, presence of heartburn, positive SPT to food or aeroallergens, diet institution date, disease duration, peak eosinophil level, and endoscopic features. The study was approved by the Institutional Review Board at Northwestern University. Informed consent was obtained from all patients for study enrollment.

Results

Patient Characteristics and Clinical Features

Fifty patients (25 men) completed the initial 6-week SFED treatment period, and 20 patients completed the reintroduction process. Demographics are listed in Table 1. Thirty patients were not included in the analysis of the reintroduction process because of a lack of adequate response or incomplete data acquisition for the following reasons: nonresponse (8), partial response (7), moved out of state (3), and still completing the reintroduction process (12). Forty-two of 50 patients were on twice-daily PPIs at the time of index EGD. The remaining 8 patients underwent 24-hour pH testing with normal distal acid exposure. Four patients

Table 1. Patient Demographics and Clinical Characteristics

	Patients completing the SFED (N = 50)	Patients completing reintroduction (N = 20)
Mean age, *y* (*range*)	40 (19–76)	40 (22–55)
Presenting symptom		
Dysphagia	48/50 (96%)	19/20 (95%)
Food impaction	37/50 (74%)	13/20 (65%)
Heartburn	47/50 (94%)	15/20 (75%)
Duration of symptoms (*range*)	6 y (3 mo to 25 y)	9 y (1–25 y)
Endoscopy features		
Concentric rings	49/50 (98%)	18/20 (90%)
Linear furrows	33/50 (66%)	15/20 (75%)
Stricture	18/50 (36%)	8/20 (40%)
Exudates/plaques	15/50 (30%)	10/20 (50%)
Ethnicity		
Caucasian	49/50 (98%)	20/20 (100%)
African American	1/50 (2%)	
Presence of atopy (asthma, allergic rhinitis, allergic conjunctivitis, sinusitis, or eczema)	41/50 (82%)	18/20 (90%)
Family history		
Dysphagia	10/50 (20%)	4/20 (20%)
Eosinophilic esophagitis	2/50 (4%)	1/20 (5%)
Atopy	12/50 (24%)	6/20 (30%)
Any combination of these	4/50 (8%)	2/20 (10%)
Skin prick test results		
Isolated foods	5/50 (10%)	3/20 (15%)
Isolated aeroallergens	15/50(30%)	7/20 (35%)
Both	20/50 (40%)	4/20 (20%)
Neither	10/50 (20%)	6/20 (30%)
Common food allergens on skin prick test[a]		
Nuts	26/50(52%)	11/20 (55%)
Wheat	10/50 (20%)	4/20 (20%)
Soy	10/50 (20%)	4/20 (20%)
Seafood	6/50 (12%)	3/20 (15%)
Egg	6/50 (12%)	3/20 (15%)
Milk	3/50 (6%)	1/20 (5%)
Common aeroallergens on skin prick test[a]		
Tree	30/50 (60%)	11/20 (55%)
Grass	25/50 (50%)	8/20 (40%)
House dust mite	22/50 (44%)	7/20 (35%)
Ragweed	20/50 (40%)	7/20 (35%)
Cockroach	18/50 (36%)	5/20 (25%)
Mold	16/50 (32%)	7/20 (35%)
Cat	16/50 (32%)	5/20 (25%)
Dog	5/50 (10%)	0/20 (0%)
Feather	7/50 (14%)	1/20 (5%)

[a]Percentages are based on patients who had a positive SPT. Percentages do not add up to 100% because some patients tested positive to multiple agents.

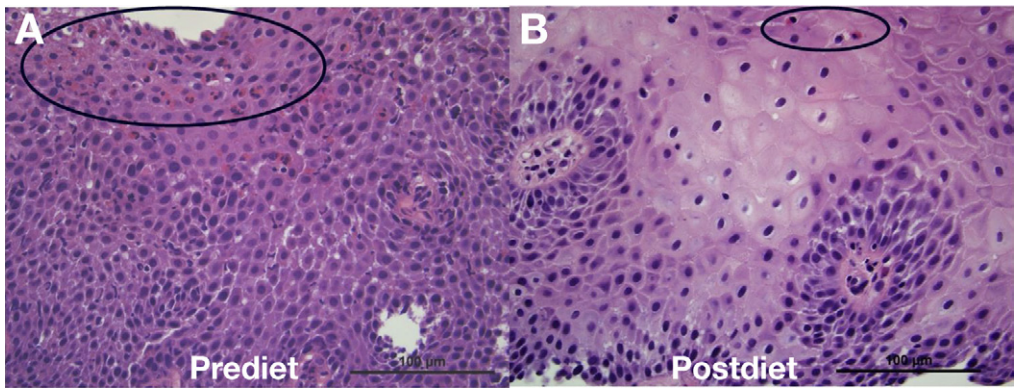

Figure 1. Histomicrograph of H&E staining of an esophageal biopsy specimen from patient with EoE. (*A*) Histologic features of EoE in the patient before institution of the SFED. Characteristic features of EoE are present including >15 eosinophils/hpf, superficial layering, eosinophilic microabscesses, and epithelial hyperplasia. (*B*) Resolution of histologic features of EoE in the same patient after completion of 6 weeks of the SFED (original magnification, 400×).

had been tried on topical corticosteroids without clinical or histologic response before the study. Topical corticosteroids had been discontinued at least 8 weeks before the study, and these patients had an index endoscopy with histology showing esophageal eosinophilia before inclusion in the study. All other patients were treatment-naive.

Histologic and Clinical Response

Before treatment, eosinophil levels were higher in the distal than proximal esophagus ($P = .005$). Peak eosinophil counts in biopsy specimens for the cohort had a mean value of 53 eos/hpf (range, 17–108 eos/hpf) before treatment. Paired biopsy samples were compared from the proximal and distal esophagus from each patient at the index endoscopy, after 6 weeks of SFED, and in those who underwent reintroduction. Peak eosinophil densities decreased significantly after SFED in both the proximal and distal esophagus (Figure 1). Proximally, the mean peak eosinophil density declined from 34 to 8 eos/hpf ($P < .0001$). Distally, the mean peak eosinophil density declined from 48 to 13 eos/hpf ($P < .0001$) (Figure 2*A* and *B*). Data then were analyzed separately for the complete responder, partial responder, and nonresponder groups. In the patients with a complete response, the mean peak eosinophil density decreased from 32 to 3 and 48 to 3 in the

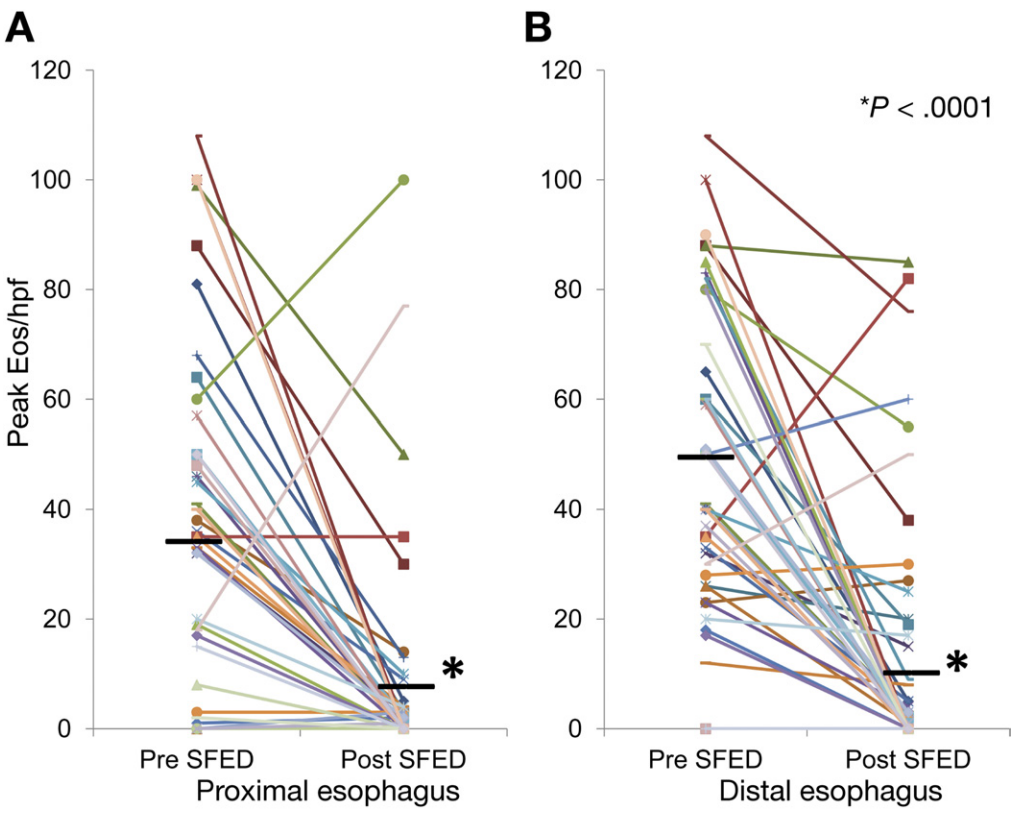

Figure 2. (*A*) Peak eosinophil counts in the proximal esophagus before and after 6 weeks of the SFED (N = 50). (*B*) Peak eosinophil counts in the distal esophagus before and after 6 weeks of the SFED (N = 50).

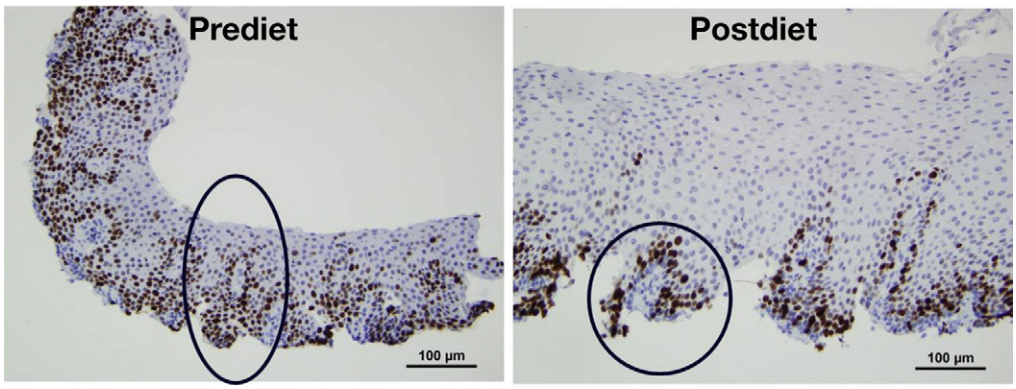

Figure 3. Reduction of immunohistochemical staining of ki-67 in an esophageal biopsy from patient with EoE. *Left*: more diffuse staining throughout all layers of the biopsy specimen before the SFED, correlating with increased cell proliferation. *Right*: reduction of ki-67 staining after SFED and staining only in the basal layer as expected.

proximal and distal esophagus, respectively ($P < .0001$). The mean pretreatment and post-treatment values in partial responders were 59 and 9 in the proximal esophagus and 50 and 16 in the distal esophagus, respectively. The mean pretreatment and post-treatment values in nonresponders were 42 and 30 in the proximal esophagus and 62 and 55 in the distal esophagus, respectively.

After the 6-week SFED treatment period, 64% of patients had ≤5 eos/hpf, 70% had ≤10 eos/hpf, 74% had ≤15 eos/hpf, and 78% of patients had >50% reduction in their peak eosinophil density. We looked further at effect sizes for these decreases, which were d = 0.79 (proximal) and d = 1.0 (distal), suggesting that dietary intervention provided a virtually uniform improvement in eosinophil counts for those engaging in the diet elimination protocol. Biopsy specimens in responders also showed decreased ki-67 staining from 53% to 7% after the SFED ($P = .003$) (Figure 3).

Dysphagia symptom scores decreased in 94% of patients after the SFED with median scores going from 12 to 3.5 ($P < .0001$) (Figure 4). The individual dysphagia score components were analyzed. The dysphagia frequency score decreased from 3.5 to 2 ($P = .04$). The dysphagia intensity score decreased from 3.4 to 1.8 ($P = .003$), and the dysphagia duration score decreased from 2.2 to 1 ($P = .03$). The lifestyle change score decreased from 1.6 to 1.4 ($P = .52$). Subjectively, endoscopic features

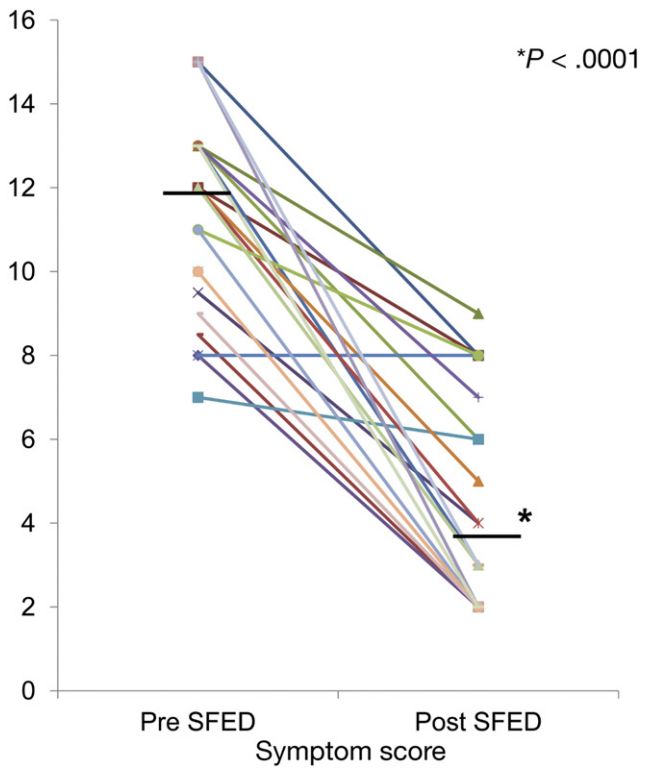

Figure 4. Dysphagia symptom scores in an EoE cohort before and after the SFED.

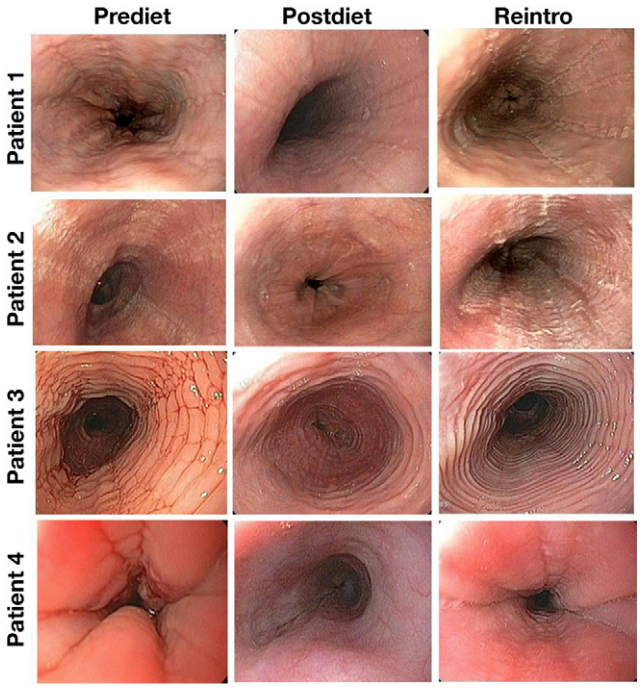

Figure 5. Characteristic endoscopic changes at baseline (*left*) improve after the SFED (*middle*), and recur with reintroduction of the trigger food (*right*). In patient 1, prominent furrows are noted at baseline, which improve with the SFED and recur upon reintroduction of wheat. In patient 2, prominent exudates and subtle rings at baseline improve after the SFED and recur after reintroduction of wheat. In patient 3, prominent rings, furrows, and edema are noted, which improve after the SFED and recur with reintroduction of milk. In patient 4, prominent furrowing and edema are noted at baseline, which resolve after the SFED and recur with reintroduction of wheat.

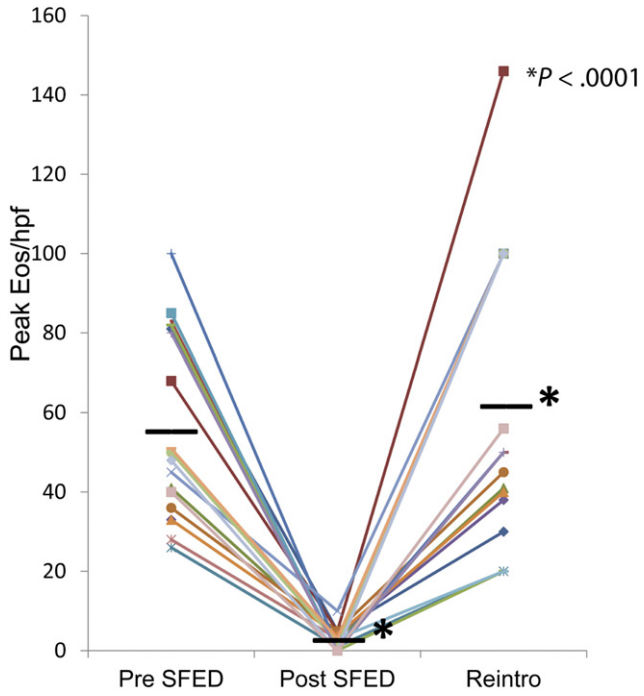

Figure 6. Peak eosinophil counts in the esophagus at baseline, after the SFED, and after reintroduction of the trigger food. After the trigger food has been encountered, peak eosinophil levels increase to close to baseline levels seen before the SFED (N = 20).

improved in 78% of patients after dietary intervention. The same endoscopists performed the index and follow-up procedures (N.G. and I.H.).

Predictors of clinical response included patients who initially had complaints of heartburn and those who began the SFED within the last 3 years of the study ($P < .05$). The odds of complete response was 7 times greater for those who instituted the diet in the last 3 years versus those who began in the first year of the study. In addition, patients with heartburn symptoms had 5 times the odds of response compared with those who did not. Although male sex, age, increased eosinophil density, and the presence of furrows and exudates suggest a trend toward increased likelihood of response, and the presence of endoscopic rings and strictures suggest a trend to decreased likelihood of response, these did not reach statistical significance. The presence of atopy, positive skin testing to food allergens, and positive skin testing to aeroallergens did not predict a complete response.

Reintroduction of Trigger Foods

The causative food agent was found in all 20 patients who completed the reintroduction process. All patients had symptom recurrence, histologic recurrence, and endoscopic abnormalities after exposure to the causal agent, with median time to symptom recurrence of 3 days. Furthermore, reintroduction of the causal agents was associated with recurrence of esophageal abnormalities on EGD (Figure 5). The mean peak eosinophil densities before and after food reintroduction were 2 and 61, respectively ($P < .0001$) (Figure 6). This observation did not vary by biopsy location: mean peak eosinophil densities before and after food reintroduction were 3 and 45 in the proximal and 3 and 48 in the distal biopsy specimens, respectively ($P < .0001$). The most common food triggers were wheat (60%) and milk (50%), followed by soy (10%), nuts (10%), and egg (5%). No patient had seafood as an identified trigger. Three patients had more than one food trigger. Interestingly, SPT accurately predicted only 13% of causal agents, and 67% of patients who had a food trigger identified by the reintroduction process had a negative SPT to all foods.

Impact on Quality of Life

QOL metrics based on SF-36 scores were obtained at baseline and immediately after completing the SFED. Compared with the general population, patients with EoE had slightly improved physical scores but slightly decreased mental scores; however, this was not statistically significant. Both physical and mental components increased after the SFED with the greatest change in the physical component in women. Although individual physical component scores tended to improve after the SFED for both men and women, individual mental scores decreased. There was a significant decrease in role emotion in men and women and in social function in men.

Discussion

Our prospective study showed a high degree of effectiveness of the SFED in the treatment of both symptoms and histopathology in adults with EoE.[20] Seventy-eight percent of patients achieved greater than a 50% reduction in peak eosinophil counts, with 70% achieving ≤10 eos/hpf and 64% achieving ≤5 eos/hpf after treatment. Coinciding with resolution in pathology, dysphagia symptom scores improved significantly after the SFED. The systematic reintroduction of food in patients who achieved an initial complete response to the diet identified causative dietary agent(s) in all patients. Reintroduction of causative foods resulted not only in recurrence of esophageal eosinophilia but also symptoms and endoscopic abnormalities. Fifteen percent of patients had more than one food trigger identified, with the most common triggers being wheat (60%) and milk (50%).

In a previous study of the SFED in children with EoE, Kagalwalla et al[10] showed a 74% histologic response and 97% symptom response. By using the same treatment protocol in the current study, the 70% histologic response and 94% symptom response in the adult cohort was comparable, suggesting that, similar to children, food allergens have a causative role in the majority of adults with EoE. Furthermore, the results of the reintroduction process support that food antigens are driving this response, providing new insight into the nature of the inflammatory response in adult EoE. This study also suggests that despite the phenotypic differences of adult and pediatric EoE, the pathophysiology of this disease is likely similar in the 2 patient cohorts. Our observation of the most common trigger foods are also supported by similar find-

ings in pediatric cohorts. Kagalwalla et al[13] showed that the 2 most common foods found to trigger a response during their reintroduction protocol were milk in 74% and wheat in 26%. Milk and wheat were also the most common foods found to trigger a response by skin prick testing and patch testing as well as by rechallenge in a large pediatric series.[21]

All patients had recurrence of their symptoms within 5 days of adding the trigger food with a median time to recurrence of 3 days. This is similar to data in children in whom food challenges re-created symptoms within 24 hours.[8] Interestingly, none of our patients provided a history of food allergies or intolerance to these foods before enrollment in the study. In most cases, patients underwent EGD within 1–2 weeks of symptom recurrence. Both endoscopic and histologic inflammatory responses were evident, objectively supporting the recrudescence of disease activity. After a recurrence, patients underwent a washout period of the trigger food for 6 weeks followed by repeat endoscopy showing resolution of histologic eosinophilia, also supporting the association of a food allergy–driven response.

Of note, approximately a third of EoE patients in both the previously reported pediatric and current adult study did not achieve the histologic goal of ≤10 eos/hpf and ≤5 eos/hpf, respectively. This may reflect reactivity to dietary allergens not included in the SFED, cross-contamination, lack of adherence to the diet, or, potentially, an aeroallergen stimulus. Of the nonresponders in our study, 2 patients repeated the SFED with stricter control, 1 patient completed an elemental diet, and all 3 patients had complete response (data not shown). In our study, aeroallergens were not treated concomitantly and therefore may have contributed to the lower response rate.

The role of allergy testing in the management of EoE in adults is unclear. SPT was predictive in only 13% of patients, and 67% of patients who were found to have a food trigger tested negative to all food allergens. Although larger numbers will be needed to validate this finding, this does suggest that SPT may not be as helpful in adults as in children.[12] Atopy patch testing may have a higher yield compared with SPT, but was not studied in our patients.

Significant predictors of response included patients who initially had complaints of heartburn and those who began the diet several years after the study began. Heartburn was reported by patients despite acid suppression with twice-daily PPIs, arguing strongly that the symptom was not a manifestation of acid reflux. Instead, it is possible that heartburn is a manifestation of an allergic response to foods. Another possibility is that the symptom of heartburn may be owing to esophageal hypersensitivity in EoE patients as described in a recent study.[22] The higher success rate in patients enrolled in the latter half of the study may be explained by more intensive dietary education that occurred with experience. This also could be owing to the fact that early in the study, dietary education was provided in a group format, whereas as the study progressed, dietary education was provided in individual training sessions. As the study progressed, patients had direct access to a dietitian dedicated to this study via e-mail and telephone. Patient education materials also were updated to reflect our adult population. This suggests that individual dietary education sessions may be more effective to achieving success on the diet. Other factors that may have played a role include increased access to food items and improved allergen labeling at subspecialty grocery stores as the study period progressed.

Male sex, age, increased eos/hpf, and the presence of furrows and exudates showed a trend toward increased likelihood of dietary response. Similarly, the presence of endoscopic rings and strictures decreased the likelihood of a dietary response. This suggests that perhaps patients with a more inflammatory phenotype such as furrows and exudates are more likely to respond than those with more fibrotic/fixed changes such as rings or strictures. Surprisingly, patients with a history of atopy or positive allergy testing were no more likely to respond to the diet.

In addition to histologic resolution of esophageal eosinophilia in our patients, additional histologic findings of immunohistochemical staining for ki-67, a cell proliferation marker, also diminished. Epithelial hyperplasia also subjectively decreased. Although current natural history studies suggest that there is no progression of epithelial hyperplasia to malignancy in EoE, these studies have had a short duration of follow-up evaluation.[16] Prior studies have shown that treatment with topical steroids has reversed findings of epithelial hyperplasia, measured by ki-67, in children with EoE after treatment with topical corticosteroids.[17,18] Our present study also shows this effect after treatment with dietary therapy.

This study addressed QOL in adults with EoE undergoing therapy.[23] By using the SF-36, there was no overall difference in physical or mental well-being in EoE adults compared with controls. Although physical component scores improved after the SFED, specific elements of the mental component score decreased. There was a decrease in role emotion in men and women and a decrease in social function in men. During this 6-week interval, patients were urged not to eat at restaurants and to bring their own food to work to avoid cross-contamination. This may have had an impact on social well-being for some patients. These follow-up QOL scores were obtained after 6 weeks on the SFED when limitations were most strict. We suspect that if QOL was assessed after patients completed the reintroduction process, scores would improve. The use of a generalized disease measure also may not be ideal to assess QOL in EoE but was the only measure available at the start of this study. Based on our preliminary data, our center has since developed a disease-specific QOL measure in adults with EoE and using this measure after interventions may be more meaningful.[24]

Although these results provide new insight into the pathogenesis of EoE in adults and provide a novel treatment approach, we acknowledge several limitations to the study. This was an uncontrolled study so there may have been a selection bias in patients who were willing to undergo di-

etary elimination. This patient cohort had a higher percentage of women than typically reported in the literature, which may also represent patient selection bias with women being more willing to try dietary intervention. Although this was an effective intervention at controlling the symptoms, histology, and endoscopic features of EoE, it is unclear if this is a feasible long-term therapy for adults and a maintenance arm of this study is ongoing to answer this question. Although it is known that EoE can induce remodeling and fibrosis, which can reverse with therapy, we did not have enough subepithelial tissue in our paired samples to analyze this effect systematically. Finally, our primary end point was defined as a maximum eosinophil level of ≤5. Although the optimal target end point of treatment remains to be defined, a peak eosinophil count of ≤5 has been a commonly used end point in prior clinical studies and therefore was used.

Another important point to note is that although the SFED has been shown to be highly effective in children and now in adults, it may not achieve the same degree of histologic remission as patients placed on an elemental diet as was shown in pediatric studies.[8–10] Although many of our responders did have 0 eos/hpf after treatment, some did have levels in the 1–5 eos/hpf range. Although the optimal target treatment end point remains to be defined, the benefit of the SFED in terms of palatability, cost, and ease of administration may outweigh the potential limitations placed on adults ingesting an elemental diet. Further comparative studies between an elemental diet and the SFED in adults need to be undertaken to better address this question.

In conclusion, an empiric diet eliminating common food allergens was highly effective at inducing histologic, endoscopic, and symptomatic improvement in the majority of adult patients with EoE. This study prospectively investigated the usefulness of an empiric, elimination diet with systematic reintroduction of food allergens and implicates food allergens in the pathogenesis of EoE in adults. The findings support a common pathophysiologic mechanism for children and adults with EoE, despite different phenotypic presentations. The systematic reintroduction of foods was able to identify patients' specific food triggers, further supporting the role of food allergens driving this antigenic response. Given the poor sensitivity of SPT and lack of history of food allergy or intolerance, the SFED with reintroduction is the only reliable method to date to identify food triggers in adult EoE and should allow us to better tailor the diet to individual patients for long-term management. An empiric elimination diet with identification of specific food triggers is an effective therapeutic alternative to corticosteroids for adults with EoE.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi:10.1053/j.gastro.2012.03.001

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Conflicts of interest

The authors disclose no conflicts.

Appendix A

Dysphagia Symptom Score[16]

Frequency

0___No attacks during the past year
1___1 or 2 attacks per year
2___1 attack/3 months
3___1 attack/month
4___1 attack/week
5___1 attack/day

Intensity

1___Swallowing unhindered and without pain
2___Slight retching disappearing spontaneously
3___Short periods of obstruction needing intervention such as drinking, deep breathing, retching, and so forth
4___Longer-lasting obstruction only removable by vomiting
5___Continuous complete obstruction requiring endoscopy for removal

Duration

0___No attacks
1___<1 minute
2___1–10 minutes
3___11–60 minutes
4___Several hours
5___Lasting until endoscopy removed food

Lifestyle changes

0___Absent
1___Minor (alter food intake by texture/consistency, no solid food without liquid, and so forth)
2___Major (job change, reducing social contacts, and so forth)

Appendix B

Endogenous peroxidase activity was quenched in paraffin-embedded tissue sections with 1% H_2O_2. Antigen was retrieved by pretreatment with citrate buffer in a microwave. Nonspecific protein-protein interactions were blocked with diluted normal serum. The slides were incubated with 1 ug/mL Ki-67 antibody (Vector, Burlingame, CA), followed by the appropriate biotinylated secondary antibody and the avidin-biotin-peroxidase complex for 45 minutes each. Diaminobenzidine was used as the chromogen. Negative controls were established by replacing the primary antibody with phosphate-buffered saline and normal serum.

Appendix C

Effect size guidelines specify the following: minimal to no effect, 0.00–0.19; small effect, 0.20–0.49; medium effect, 0.50–0.79; and large effect, $\geq$0.80.[19]