see related editorial on page 1474

Influence of Age and Eosinophilic Esophagitis on Esophageal Distensibility in a Pediatric Cohort

Calies Menard-Katcher, MD, MS[1,2], Alain J. Benitez, MD[3], Zhaoxing Pan, PhD[4], Faria N. Ahmed, BA[1], Benjamin J. Wilkins, MD, PhD[5], Kelley E. Capocelli, MD[6], Chris A. Liacouras, MD[7,8], Ritu Verma, MD[7,8], Jonathan M. Spergel, MD, PhD[3,8], Glenn T. Furuta, MD[1,2] and Amanda B. Muir, MD, PhD[7,8]

OBJECTIVES: **Sequelae of eosinophilic esophagitis (EoE) include food impaction and esophageal stricture. Duration of inflammation is a predicted risk factor; however, complications remain unpredictable. Studies using the functional lumen imaging probe (FLIP) have demonstrated decreased distensibility of the esophagus in adult patients with EoE. As the impact of inflammation on the developing esophagus is unknown, we investigated esophageal distensibility in a pediatric cohort to determine the effect of age, ongoing inflammation, and fibrotic features on distensibility.**

METHODS: **We conducted a prospective observational study at two tertiary pediatric institutions. Subjects underwent FLIP evaluation during endoscopy to determine distensibility of the esophagus. During stepwise distension, simultaneous intrabag pressure and 16 channels of cross-sectional areas were measured. The minimal diameter at maximal esophageal distention at an intrabag pressure of 40 mm Hg was identified. Distensibility was compared between EoE and non-EoE subjects and between clinical variables within the EoE cohort. Potential confounding variables were identified.**

RESULTS: **Forty-four non-EoE and 88 EoE subjects aged 3–18 years were evaluated. Age positively correlated with esophageal distensibility in the non-EoE cohort, but this trend was not observed in the EoE population. Subjects with EoE had reduced distensibility even after adjusting for age. Active inflammation (eosinophils >15 eos/high-power field), histological lamina propria fibrosis, and various features of a fibrotic phenotype (stricture, food impaction, circumferential rings on endoscopy) were associated with decreased distensibility within the EoE cohort. FLIP was safe, feasible, and well tolerated.**

CONCLUSIONS: **These findings suggest that remodeling occurs in the pediatric EoE population, warranting early diagnosis and initiation of therapy prior to the onset of disease complications.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

Am J Gastroenterol 2017; 112:1466–1473; doi:10.1038/ajg.2017.131; published online 16 May 2017

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic immune-mediated disease of the esophagus. EoE often results in chronic esophageal inflammation, tissue remodeling, fibrosis, and clinical outcomes of swallowing dysfunction and stricture. Natural history studies suggest that, after years of chronic inflammation, stricture may be inevitable (1,2). In fact, up to 67% of adult patients have fibrostenotic features, often defined as having circumferential rings of the esophagus or esophageal stricture. These findings are less common in pediatric patients, reported to be in 16% of pediatric

[1]Digestive Health Institute, Gastrointestinal Eosinophilic Diseases Program, Children's Hospital Colorado, Aurora, Colorado, USA; [2]Section of Pediatric Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Mucosal Inflammation Program, University of Colorado School of Medicine, Aurora, Colorado, USA; [3]Division of Allergy and Immunology, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA; [4]Research Institute, The Children's Hospital Colorado, Department of Pediatrics, University of Colorado School of Medicine, Aurora, Colorado, USA; [5]Department of Pathology and Laboratory Medicine, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA; [6]Department of Pathology and Laboratory Medicine, Gastrointestinal Eosinophilic Diseases Program, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, Colorado, USA; [7]Division of Gastroenterology, Hepatology and Nutrition, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA; [8]Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA. **Correspondence:** Calies Menard-Katcher, MD, MS, Children's Hospital Colorado, 13123 E. 16th Avenue, B290, Aurora, Colorado 80045, USA or Amanda B. Muir, The Children's Hospital of Philadelphia, 34th and Civic Center Boulevard, Philadelphia, Pennsylvania 19103, USA. E-mail: calies.menard-katcher@childrenscolorado.org or muira@email.chop.edu
Received 29 November 2016; accepted 28 March 2017

patients with EoE (3). As evidence suggests treatment can minimize the development of fibrostenosis, early detection and treatment of EoE in the pediatric EoE population could lead to better outcomes and decreased fibrostenotic disease in adulthood.

Current methods of detecting fibrotic remodeling, particularly at its early stages, are limited by reliability and feasibility. Mucosal pinch biopsies do not always capture the esophageal submucosa, thus making the assessment of lamina propria fibrosis unpredictable. When the submucosa is captured, interpretation of lamina propria fibrosis is challenging and vague (4,5). Endoscopic evaluation itself may in fact underestimate clinically significant narrowing of the esophagus (6,7). Barium swallow studies may be more accurate in detecting abnormalities but these tests have their own limitations, particularly in the pediatric population (7). Perhaps the greatest limitations of endoscopic and radiological evaluations are that they detect fibrostenosis late in the course of pathological remodeling.

The endoluminal functional lumen imaging probe (FLIP) is an endoscopic tool that determines the pressure–geometry relationship or distensibility of hollow gastrointestinal organs, including the esophagus. FLIP has been utilized diagnostically and therapeutically in the management of gastroesophageal reflux and bariatric surgery (8,9). More recently, FLIP provided valuable information in the evaluation of adults with EoE. Studies examining the adult esophagus show that patients with EoE have decreased distensibility compared with control patients (10,11). However, nothing is known regarding pediatric esophageal distensibility and the effects of inflammation on distensibility in children. Our study sought to determine whether the FLIP can identify early remodeling in pediatric EoE. We hypothesized that distensibility would be influenced by age and decreased in children with EoE.

METHODS

Study design

We conducted a prospective observational study at two tertiary pediatric hospitals to examine the correlation of distensibility with age and other clinical variables in a normal pediatric population and to examine the difference in distensibility between control subjects (without esophageal pathology) and subjects with EoE. This study was approved by the internal review board at each institution.

Study subjects

Subjects aged 3–18 years undergoing upper endoscopy for the evaluation of clinical symptoms or management of EoE were eligible for enrollment. Patients were not approached and were excluded from enrollment if they had a preendoscopic known history of esophageal or other gastrointestinal disease including but not restricted to anatomical abnormalities unrelated to EoE, tracheoesophageal fistula, achalasia, other eosinophilic gastrointestinal disease, inflammatory bowel disease, or history of connective tissue disease, bleeding disorder, or other chronic medical condition or if they were receiving systemic corticosteroids for any reason. EoE subjects were defined based on current clinical diagnostic guidelines (12): as having a history of esophageal symptoms and esophagitis with > 15 eosinophils per high-power field (eos/hpf) despite a trial of a proton pump inhibitor for at least 8 weeks. EoE subjects with severe esophageal stricture precluding passage of standard adult endoscopy (8.6 mm) were excluded. Subjects were included in the analysis as non-EoE controls if upper endoscopy was normal with normal esophageal and gastric biopsies. All subjects or their parents provided informed consent. Signed informed assent was obtained from the child when appropriate. All subjects underwent anesthesia conducted by a board-certified anesthesiologist.

Endolumenal functional assessment

EndoFLIP (Crospon, Galway, Ireland) (FLIP) was used to measure lumen diameter and intraballoon pressure at stepwise balloon inflation (10). Two catheters were used in the study. Prior to July of 2015, all subjects, irrespective of age or height, were studied using the available 8 cm length balloon. After July of 2015, balloon length used was determined based on patient height: generally, a 16-cm length balloon was used in subjects ≥120 cm in height, and an 8-cm length balloon was used for those <120 cm. After visual inspection of the esophagus by endoscopy, the FLIP catheter was positioned in the esophagus with the distal probe positioned at the esophagogastric junction. The endoscope was removed prior to insufflation and the probe manually held in place throughout inflation. The FLIP balloon was inflated to 10–15 ml to confirm position of the catheter and the balloon then insufflated pausing every 10 ml for 5–20 s. The balloon was inflated to either a maximal volume of 65 ml or maximal pressure of 50 mm Hg, whichever occurred first. To prevent unintended dilation, the recording unit was set to stop infusing and display an alarm message if the intrabag pressure exceeded 60 mm Hg. During the procedure, intrabag volume, pressure, and lumen diameter at 16 channels along the length of the catheter were recorded continuously. Following FLIP measurements, the balloon was deflated and the catheter removed. The endoscope was then replaced and mucosal biopsies obtained. The primary outcome, distensibility, was defined by the minimal esophageal body diameter determined at maximal esophageal distension at intrabag pressure of 40 mm Hg (11). This value was chosen based on previous work by others as it is considered to be slightly above typical swallow-associated pressure and determined to be a value sensitive enough to detect EoE-associated stiffness (10,11,13).

Endoscopic and histological assessment

The esophageal appearance was prospectively recorded by the performing physician prior to FLIP using a validated esophageal endoscopic reference scale (14). Presence of (i) edema, white plaques, and/or linear furrows was categorized as inflammatory endoscopic features and (ii) presence of rings and/or narrowing with or without inflammatory features was categorized as fibrostenotic features.

Biopsies were obtained based on standard clinical practice and included esophageal, gastric and duodenal biopsies and examination by hematoxylin and eosin stain. Esophageal biopsies were

analyzed for evidence of basal cell hyperplasia, rete peg elongation, abnormal inflammatory cell infiltrate, and lamina propria fibrosis. Lamina propria fibrosis was defined as thickened connective tissue fibers in the lamina propria. The fibers were compared with the diameter of a basal cell layer nucleus. A diagnosis of lamina propria fibrosis required the fibers be cohesive without increased diameter or fibers have a diameter equal to or greater than a basal cell layer nucleus. A score of "not applicable/evaluable" was reported for samples containing <35 μm lamina propria thickness (a superficial region that normally appears compacted) or samples where technical (crush) artifact impairs scoring (15).

Subject covariates

All subjects had stadiometry on the day of FLIP including height and weight. Gender, race, and ethnicity along with presenting symptom and reason for endoscopic assessment was recorded and fluoroscopic esophagram, if available, was reviewed. Subjects (and their parents) were questioned regarding esophageal symptoms over the preceding 30 days, including chest pain, heartburn, abdominal pain, vomiting, and trouble swallowing (16).

Statistical analysis

FLIP analysis. All recorded FLIP studies were manually reviewed by means of real-time video capture using a preset FLIP Analytics (Crospon, Galway, Ireland) low-weighted filter to identify the location of the esophagogastric junction and to assess the degree of secondary peristalsis. To subtract the esophagogastric junction, electrodes spanning 1–2 cm proximal to the esophagogastric junction (for the 8- and 16-cm catheter, respectively) and distal were excluded from next steps in the analysis. Secondary peristalsis was categorized as mild, moderate, or severe based on a semiquantitative frequency of antegrade or retrograde contraction. Severe was defined as ≥5 contractions in a 30-s period resulting in a decrease in the lumen diameter by ≥5 mm for ≥25% of inflation time. Moderate was defined as ≥2 contraction in a 30-s window for ≥25% of inflation time. Mild was any lesser degree of contraction.

To determine distensibility of the esophageal lumen, raw FLIP data were first filtered to mitigate the effect of esophageal peristalsis and respiration on intrabag pressure and lumen diameter. Data were filtered by the following means: (i) raw data were aggregated to every 5 s and (ii) the maximal diameter at each electrode and the mean intrabag pressure for each aggregate was identified. The minimum esophageal body diameter across the esophageal lumen length was then identified for each aggregate. The primary outcome was then determined by the minimal diameter at a mean intrabag pressure of 40 mm Hg (distensibility). Data were filtered and analyzed with STATA (STATA, College Station, TX).

Data analysis. SAS 9.4 (SAS Institute, Cary, NC) was the statistical software used for data analysis. The outcome variable, distensibility was tested for normality. Mean and s.e. were used to summarize the outcome. Other continuous and categorical variables are summarized using mean and s.d. and percentage of distribution, respectively. Multiple linear regression was used to examine the relationship between distensibility with clinical variables, namely, age, height, and weight. Analysis of covariance adjusting for child age was used to examine for other potential clinical or experimental confounding variables. Multiple linear regression was used to assess the difference between EoE and non-EoE controls while adjusting for identified confounding variables (i.e., patient age). Backward selection was used to determine the significance of two- or three-level interaction terms in order to find the best-fit model to explain variance in distensibility between the EoE and non-EoE cohorts. Sensitivity analysis was performed for variables, namely, catheter type, given the change in the use of catheters over the study period.

RESULTS

Study subjects

Forty-four non-EoE controls (23 males) and 88 EoE pediatric subjects (68 males) were enrolled. Median ages are 11.1 (3.0–17.8) years for non-EoE and 12.0 (4.2–18.6) years for EoE (**Table 1**). The primary indication for endoscopy in the non-EoE controls and the final diagnosis after endoscopy is depicted in **Table 2** and **Supplementary Table S1**.

Of the EoE subjects, 44 had significantly active disease (>15 eos/hpf and symptomatic), 35 were categorized as inactive (<5 eos/hpf), and 9 treated subjects were identified as intermediate (5–15 eos/hpf). Of the 44 significantly active EoE subjects, 16 were enrolled at time of diagnosis and were not on EoE-directed treatment. Of those EoE subjects on treatment, 34 were on diet elimination alone and 33 were treated with swallowed topical therapy with or without diet restriction. The five remaining subjects were diagnosed previously but non-adherent to treatment at time of enrollment.

Tolerance of procedure

No unanticipated events occurred during the study. Addition of the FLIP measurements was tolerated well with no reports of after-procedure pain in this cohort. The FLIP measurement added 4 min of procedure time on average.

Distensibility in relation to clinical variables

Given the variance in height and weight that occurs across ages, we sought to identify confounding factors in order to appropriately compare across groups. In univariate analysis, age, weight, or height were significantly and positively correlated with distensibility in the non-EoE control cohort (**Figure 1a**, **Supplementary Figure S1A–C**). Multiple linear regression analyses indicated that age was the most predictive independent variable, explaining 25% of the variability. Weight and height were highly correlated with age and did not improve predictability. The correlation of distensibility with age, weight, and height in EoE subjects was not as strong as observed in non-EoE controls. Unlike non-EoE controls, there was no significant correlation found for distensibility and age in EoE subjects. (**Figure 1b**, **Supplementary Figure S1D–F**). Although age did not have significant correlation with distensibility in the EoE population, it was maintained as a confounding variable in analysis.

Table 1. Patient characteristics

	Non-EoE (44)	EoE (88)	*P* values
Age (mean±s.d.), years	11.06±3.98	12.00±3.93	0.20
Male	22 (50.0%)	68 (77.3%)	0.003
Height, cm (mean±s.d.)	143.7±24.1	148.31±22.65	0.28
Weight, kg (mean±s.d.)	40.7±19.5	43.13±17.71	0.47
Atopic history	24 (54.5%)	74 (86.4%)	<0.001
Dysphagia, 30-day history	10 (22.7%)	27 (30.7%)	0.34
Impaction history	0	18 (20.5%)	<0.001
Stricture history	0	10 (11.4%)	0.02
PPI treatment	40 (90.9%)	76 (86.4%)	0.58
Swallowed steroid	0	33 (37.5%)	<0.001
Diet restriction	0	39 (44.3%)	<0.001
Normal endoscopy	46 (100%)	34 (38.6%)	<0.001
Inflammatory features[a]	0	37 (42.0%)	<0.001
Fibrostenotic features[b]	0	17 (19.3%)	<0.001
Eos/hpf (mean±s.d. (range))	0.0±0 (0–0)	27.9±31.6 (0–125)	<0.001
Catheter length—80 mm	28 (63.6%)	44 (50.0%)	0.19
Catheter length—160 mm	16 (36.4%)	44 (50.0%)	

EoE, eosinophilic esophagitis; Eos/hpf, eosinophils per high power field; PPI, proton pump inhibitor.
No. (%) except as noted.
[a]Edema, linear furrows, and/or white plaques on endoscopy.
[b]Circumferential rings and/or esophageal narrowing with or without inflammatory features.

Table 2. Non-EoE control clinical information

	Number
Primary presenting symptom	
Abdominal pain	21
Dysphagia/difficulty swallowing	10
Heartburn or reflux	8
Diarrhea	2
Failure to thrive/weight loss	2
Vomiting	2
Final diagnosis	
Functional abdominal pain	8
Non-erosive GERD	7
Dyspepsia	4
Lactose intolerance	3
Other[a]	6
Resolved	9
No GI follow-up	7

EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease;GI, gastrointestinal.
[a]Other included celiac disease (1), non-celiac gluten sensitivity (1), fool allergies without GI diagnosis (1), sigmoid volvulus (1) and failure to thrive due to inadequate caloric intake (2).

Adjusting for age, no additional investigated variables (e.g., gender, presenting symptom, or frequency of secondary peristalsis) were identified as confounders ($P<0.05$). However, a non-significant trend was observed in which the 8-cm balloon catheter was associated with greater distensibility in both the EoE and non-EoE cohorts (1.5 cm greater in non-EoE ($P=0.06$) and 1.15 cm greater in EoE ($P=0.10$)). Because of this observed trend and that catheter availability changed over the course of the study, a sensitivity analysis was performed with catheter type and determined not to affect the comparisons results. It was decided, however, to adjust for both age and catheter type when comparing clinical variables within the EoE cohort in order to present the most conservative comparison.

Distensibility in EoE compared with non-EoE controls

Unadjusted comparison between EoE and non-EoE controls demonstrates a significant decrease in distensibility in EoE subjects (14.95±2.66 vs. 17.24±2.56 mm, $P<0.0001$ by *t*-test). A best-fit multiple linear regression model, consisting of two main effect predictors, explains the relationship of age and presence of disease (**Figure 2a**). Adjusting for age, there was a 26% reduction in distensibility in EoE as compared with non-EoE controls (mean distensibility in non-EoE vs. EoE (17.13 mm (±s.e.m. 0.229) vs. 14.65 mm (±s.e.m. 0.229)), $P<0.0001$; **Figure 2b**). Distensibility increased by 0.33 mm per 1 year of age gained ($P=0.0001$).

Distensibility in EoE in relation to clinical variables

Adjusting for age and catheter, subjects with significantly active inflammation (eos>15 eos/hpf) had decreased distensibility as compared with those EoE subjects with inactive inflammation (eos<5 eos/hpf; mean distensibility 14.09 mm (±s.e.m. 0.37) vs. 16.07 mm (±s.e.m. 0.42), *P*-value 0.0007; **Figure 3a**). Subjects with intermediate inflammation (5–15 eos/hpf) also had intermediate distensibility (mean distensibility 14.81 mm (±s.e.m. 0.84), $n=9$) but was not found to be statistically different between either active and inactive inflammation. In addition, a history of stricture or food impaction, clinical dysphagia, fibrostenotic endoscopic features, and presence of lamina propria fibrosis on biopsy were all, respectively, associated with decreased distensibility (**Figure 3b–f**). No association was found between gender, dietary treatment, or topical steroids treatment and distensibility in EoE subjects. Eosinophil density (eos/hpf) was significantly and negatively correlated with distensibility (partial correlation coefficient 0.40, $P=0.0001$; **Figure 4**).

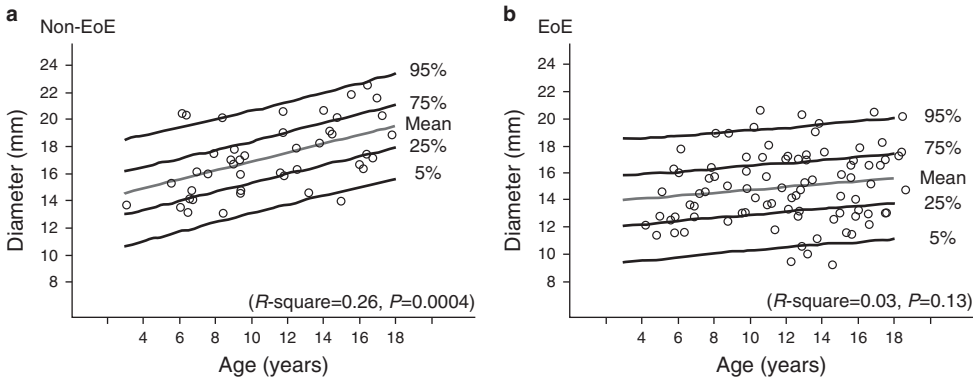

Figure 1. Regression line and prediction intervals for distensibility of the esophageal lumen across age in (**a**) non-eosinophilic esophagitis (non-EoE) controls and (**b**) EoE subjects. Distensibility significantly increases in controls but not in EoE subjects.

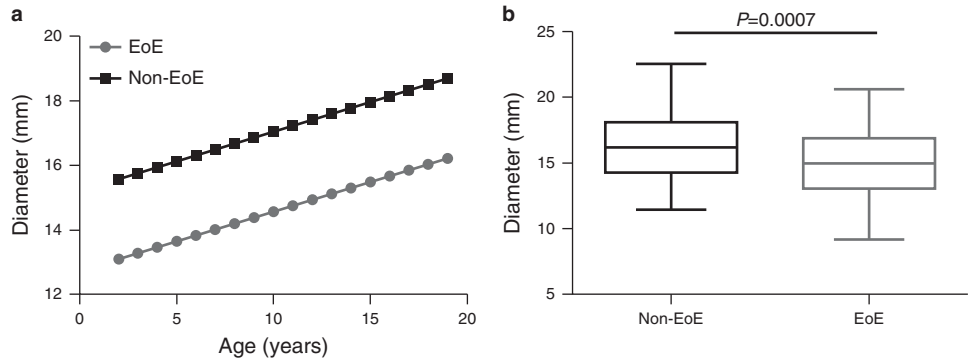

Figure 2. Predicted distensibility by age given eosinophilic esophagitis (EoE) status using a prediction model without interaction terms (best fit). Diameter increases by 0.33 mm per 1 year older. (**a**) Adjusting for age distensibility is reduced in EoE as compared with non-EoE by 26%. (**b**) Box-whisker plot for distensibility in EoE as compared with non-EoE controls.

DISCUSSION

Using the novel endoscopic tool, FLIP, we show for the first time that pediatric esophageal distensibility is significantly decreased in children with active EoE compared with non-EoE controls. In addition, a number of factors, including increased eosinophil density (>15 eos/hpf) and lamina propria fibrosis were significantly associated with this altered function. Children presenting with a history of dysphagia, food impaction, and stricture and those with ongoing dysphagia had decreased distensibility when compared with those EoE patients without these symptoms. Our data are particularly interesting as they indicate that this device can be used successfully in children and provide a feasible readout of esophageal distensibility for future studies. Moreover, we provide first values for pediatric esophageal diameter and distensibility using FLIP and insight into critical issues in the analysis of distensibility across age. Our findings suggest that the distensibility of developing esophagus can be affected by eosinophilic inflammation, thus leading to functional consequences.

Previous studies in adults with EoE have shown that reduced esophageal distensibility was associated with increased risk of food impaction and requirement of dilation (11). In this same study, the authors failed to establish any association between distensibility and eosinophil count. Although our results are consistent with their findings with regards to food impaction, we found that active inflammation was associated with decreased distensibility in this pediatric cohort. This difference may be a result of multiple contributing mechanisms of decreased distensibility, such as submucosal fibrosis vs. epithelial swelling. It may also support a theory of the "burned out" esophagus in adult EoE where there is little or variable ongoing active inflammation but instead a narrowed stiff esophagus due to chronic remodeling (1,2). Regardless, it suggests that there may be some ability to reverse or halt fibrotic remodeling when inflammation is treated effectively in children, making a strong argument in favor of early and ongoing therapy and tissue healing in patients at risk of fibrostenosis (17).

Of interest, distensibility increased with age in the non-EoE controls; however, this age effect was not significant in the pediatric EoE population. This blunting of the age effect in EoE patients may reflect fibrostenosis with increasing duration of disease leading to decreased distensibility compared with age-matched controls. Alternatively, it could reflect an underlying

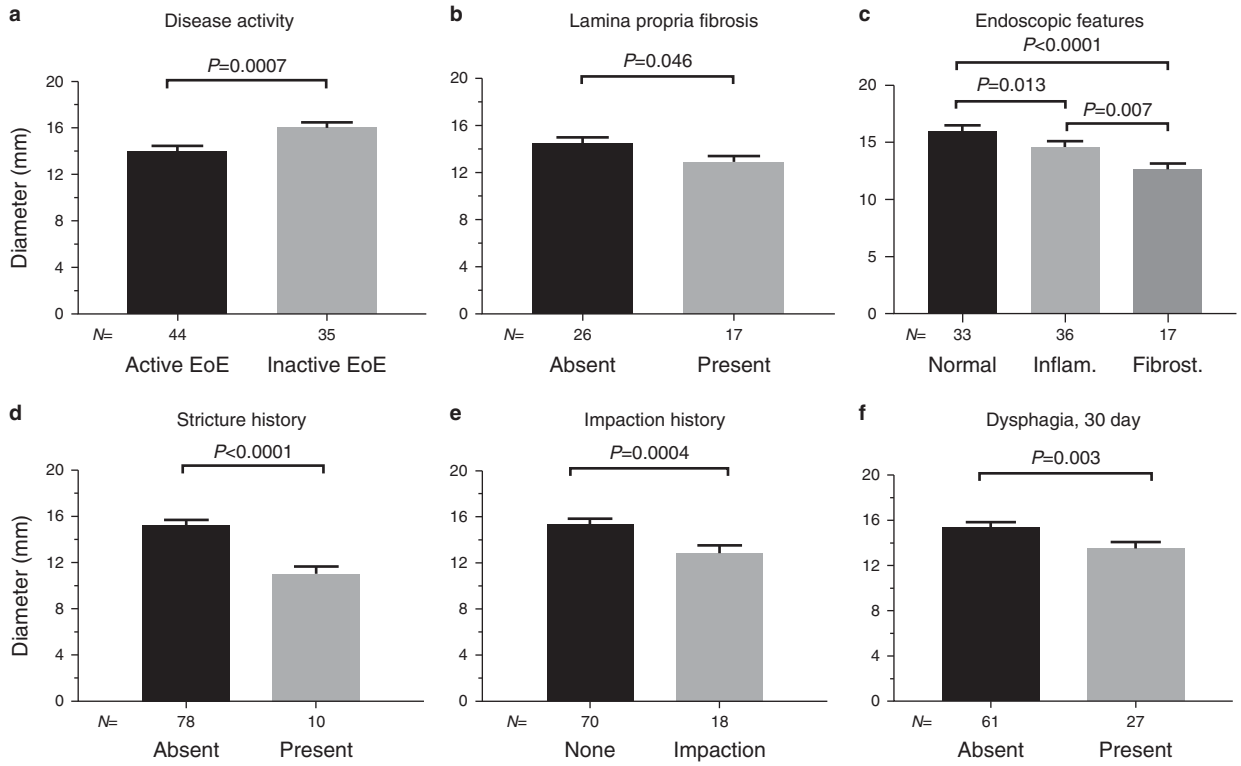

Figure 3. Distensibility in eosinophilic esophagitis (EoE) subgroups. Mean distensibility is decreased in EoE subjects with: (**a**) active inflammation (>15 eos/high-power field (hpf)) compared with those with inactive inflammation (<5 eos/hpf); (**b**) lamina propria fibrosis; (**c**) endoscopic features of fibrostenosis; (**d**) recent dysphagia; (**e**) history of food impaction; and (**f**) history of stricture. Error bars represent s.e.m. All comparisons were adjusted for age and catheter type.

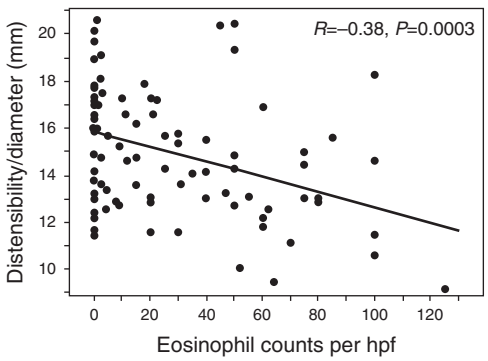

Figure 4. Lumen diameter vs. peak eosinophils per high power fields (hpfs) for all 88 eosinophilic esophagitis (EoE) patients. There is a moderate but significant negative correlation between distensibility and peak eosinophil count in EoE subjects.

fibrostenotic phenotype that assumes a less distensible pattern with or without treatment.

Decreased esophageal distensibility was associated with the presence of lamina propria fibrosis. Lamina propria fibrosis may be evidence for fibrostenotic remodeling before it becomes clinically apparent by endoscopy. However, adequate sampling of lamina propria is challenging and the clinical implications are not yet established. It has been reported that less than half of esophageal biopsies have sufficient lamina propria to evaluate for excess collagen deposition or fibrosis (5). Our findings were similar with only 48% of our EoE patients having biopsies with lamina propria deemed adequate for evaluation. FLIP, on the other hand, can be incorporated with upper endoscopy as an adjunct to visual inspection for fibrotic features and histological assessment. Our results suggest that FLIP measurements may eventually prove to be a surrogate for identifying early fibrotic disease.

During the course of our study, advances in catheter design provided two balloon lengths, an initial 8-cm balloon and a longer 16-cm balloon. Given the variability in esophageal length, we opted to continue using the 8-cm balloon in the study population <120 cm in height as it provided adequate surveillance of the pediatric esophagus and opted to use the 16-cm length balloon in taller subjects in order to provide surveillance of a greater proportion of the esophageal length. After adjusting for age, we noted a non-significant trend in both the EoE and non-EoE cohorts with the longer catheter associated with lower distensibility measurements. Although non-significant, we performed sensitivity analysis to confirm our findings were not driven by a catheter effect. An explanation for this finding is not clear. Previously published studies in EoE have used both catheter lengths but have not compared the two (11,13). Until this observed trend can be directly studied, we recommend that when following patients longitudinally the same catheter type be used and propose that consideration be given to using the 8-cm catheter in children

with an estimated esophageal length <16 cm but that, in other children and adults, the longer 16-cm catheter be used in the evaluation of lumen distensibility in EoE.

There has been an evolution in the means FLIP data are analyzed (13). In future, validation of methods to use FLIP in defining the esophageal volume instead of the single worst region of poor esophageal distensibility may prove valuable. In clinical practice, a finding of poor distensibility could be a result of very different esophageal findings. In one case, an EoE patient may have a short segment stricture with a focal area of poor distensibility. In contrast, a second EoE patient may have a long segment small-caliber esophagus but with a similar esophageal distensibiity throughout. In our current study, the distensibility in these two examples may be similar and important; however, the information obtained by evaluating the esophageal volume over a consistent catheter length may provide even more useful information with regard to pathophysiology, chronic disease, and treatment approaches.

The strengths of this study include the first use of FLIP comparing children with EoE to non-EoE controls, the large sample size, enrollment of subjects from two centers, and the assessment across all pediatric age groups. We have performed the FLIP on >100 pediatric patients undergoing endoscopy and we found that it is safe and feasible with no side effects or increased risk. In addition, we describe a novel method for FLIP analysis utilizing widely available statistical packages, making this a procedure that could be practically performed at any endoscopy center.

In interpreting our findings, we recognize a few points that should be considered. Our control group were not necessarily "normal" as all subjects were undergoing endoscopy for clinical purpose and the majority were on proton pump inhibitor. Our control group may have included patients with proton pump inhibitor-responsive esophageal eosinophilia, although to the best of our knowledge that is not the case (**Table 2**, **Supplementary Table S1**). Second, although not a significant difference, a greater proportion of controls were studied using the 8-cm balloon. A sensitivity analysis of catheter type did not find this variable to influence results. However, given the observed trend between catheter types on distensibility, we opted to adjust for both age and catheter type when comparing clinical variables within EoE subjects. Although this was considered to be a more conservative approach, this may have affected our comparisons in unforeseen ways.

Tissue remodeling and fibrosis can lead to poor patient outcomes in EoE, including stricture and food impaction. Although duration of inflammation is a leading risk factor, the progression to these outcomes is unpredictable and chronic treatment appears to decrease likelihood of fibrostenotic complications. We demonstrate for the first time that the diseased esophagus has decreased distensibility in a pediatric cohort with EoE, and in contrast to adult studies, treated EoE with low eosinophil density was associated with improved distensibility. Two important implications arise from these results: (i) controlling inflammation may improve distensibility and (ii) there may exist a critical window where treatment aimed at reducing inflammation has a greater opportunity to prevent or reverse fibrostenotic disease. FLIP provides a novel means to provide a functional assessment of pediatric EoE and it is our hope that this will aid clinicians in better understanding the response to therapy and prevent or improve life-long swallowing dysfunction. Future studies will continue to address these questions.

ACKNOWLEDGMENTS

We thank the endoscopy suite staff, faculty, and fellows in the Children's Hospital of Philadelphia Division of GI, Hepatology, and Nutrition and Children's Hospital Colorado Section of GI, Hepatology and Nutrition for their time, support, and technical assistance with the study. We also thank the Suzi and Scott Lustgarten Center for GI Motility for their generosity and support.

CONFLICT OF INTEREST

Guarantors of the article: Amanda B. Muir, MD and Calies Menard-Katcher, MD, MS.

Specific author contributions: Experimental design: C.M.K., A.B.M., A.J.B., J.M.S. and G.T.F.; experimental execution: A.J.B., F.N.A., A.B.M., C.M.K., G.T.F. and C.L.; data analysis and interpretation: P.Z., C.M.K., A.B.M., A.J.B. and G.T.F.; reagents/materials/analysis tool contributions: A.B.M., C.M.K., A.J.B., G.T.F., B.J.W. and K.C., R.V.; manuscript writing/editing: A.B.M., C.M.K., B.J.W., K.C., C.L., G.T.F., J.M.S., P.Z. and R.V.

Financial support: This study was supported by the following NIH Grants: K08DK106444 (A.B.M.), K23DK109263 (C.M.K.), AGA June and Donald AGA Castell Esophageal Clinical Research Award (A.B.M.), NASPGHAN George Ferry Young Investigator Development Award (C.M.K.), and NIH 1K24DK100303 (G.T.F.). CEGIR (U54 AI117804) is part of the Rare Disease Clinical Research Network (RDCRN), an initiative of the Office of Rare Disease Research (ORDR), NCATS, and is funded through collaboration between NIAID, NIDDK, and NCATS (G.T.F., A.B.M., Z.P., K.C., J.S. and C.M.K.) CEGIR is also supported by patient advocacy groups including APFED, CURED and EFC.

Potential competing interests: G.T.F.: EnteroTrack, Royalties recieved from UptoDate. The other authors declare no conflict of interest.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Eosinophilic esophagitis (EoE) is a chronic inflammatory disease that effects children of all ages.
- ✓ Little is known about the natural history of EoE or the effects of chronic inflammation on the distensibility of the esophagus.

WHAT IS NEW HERE

- ✓ Esophageal distensibility increases with age in the normal pediatric population.
- ✓ Esophageal distensibility is decreased in pediatric EoE patients.
- ✓ There is decreased distensibility in patients with increased disease activity and lamina propria fibrosis.

REFERENCES

1. Schoepfer AM, Safroneeva E, Bussmann C *et al.* Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. Gastroenterology 2013; 145:1230–6.e1-2.
2. Dellon ES, Kim HP, Sperry SL *et al.* A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. Gastrointest Endosc 2014;79:577–85.e4.
3. Singla MB, Chehade M, Brizuela D *et al.* Early comparison of inflammatory vs. fibrostenotic phenotype in eosinophilic esophagitis in a multicenter longitudinal study. Clin Transl Gastroenterol 2015;6:e132.
4. Chehade M, Sampson HA, Morotti RA *et al.* Esophageal subepithelial fibrosis in children with eosinophilic esophagitis. J Pediatr Gastroenterol Nutr 2007;45:319–28.
5. Wang J, Park JY, Cheng E. The prevalence of lamina propria and subepithelial fibrosis in mucosal biopsies with esophageal eosinophilia. JPGN 2015;2(suppl):61.
6. Gentile N, Katzka D, Ravi K *et al.* Oesophageal narrowing is common and frequently under-appreciated at endoscopy in patients with oesophageal eosinophilia. Aliment Pharmacol Ther 2014;40:1333–40.
7. Menard-Katcher C, Swerdlow MP, Mehta P *et al.* Contribution of esophagram to the evaluation of complicated pediatric eosinophilic esophagitis. J Pediatr Gastroenterol Nutr 2015;61:541–6.
8. Snow R, O'dea J. Does intraoperative gastric band adjustment to a tarteted stoma size improve weight loss? Bariatric Times 2012;9:10–12.
9. Kwiatek MA, Kahrilas K, Soper NJ *et al.* Esophagogastric junction distensibility after fundoplication assessed with a novel functional luminal imaging probe. J Gastrointest Surg 2010;14:268–76.
10. Kwiatek MA, Hirano I, Kahrilas PJ *et al.* Mechanical properties of the esophagus in eosinophilic esophagitis. Gastroenterology 2011; 140:82–90.
11. Nicodeme F, Hirano I, Chen J *et al.* Esophageal distensibility as a measure of disease severity in patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2013;11:1101–1107.e1.
12. Liacouras CA, Furuta GT, Hirano I *et al.* Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol 2011;128:3–20.e6.quiz;21–22.
13. Carlson DA, Lin Z, Hirano I *et al.* Evaluation of esophageal distensibility in eosinophilic esophagitis: an update and comparison of functional lumen imaging probe analytic methods. Neurogastroenterol Motil 2016;28:1844–53.
14. Hirano I, Moy N, Heckman MG *et al.* Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. Gut 2013;62:489–95.
15. Collins MH, Martin LJ, Alexander ES *et al.* Newly developed and validated eosinophilic esophagitis histology scoring system and evidence that it outperforms peak eosinophil count for disease diagnosis and monitoring. Dis Esophagus 2016;30:1–8.
16. Franciosi JP, Hommel KA, Greenberg AB *et al.* Development of the Pediatric Quality of Life Inventory Eosinophilic Esophagitis module items: qualitative methods. BMC Gastroenterol 2012;12:135.
17. Andreae DA, Hanna MG, Magid MS *et al.* Swallowed fluticasone propionate is an effective long-term maintenance therapy for children with eosinophilic esophagitis. Am J Gastroenterol 2016;111: 1187–97.