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Influence of age and eosinophilic esophagitis on esophageal distensibility in a pediatric cohort

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Abstract

Background and Aims—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. Since the impact of inflammation on the developing esophagus is unknown, we investigated esophageal

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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 mmHg 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/hpf), histologic 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.

Keywords

Eosinophilic Oesophagitis; Distensibility; FLIP; fibrostenosis

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 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 radiologic 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 to 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 age 3 to 18 years of age 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 pre-endoscopic known history of esophageal or other gastrointestinal disease including but not restricted to anatomic 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) (FLIP) was used to measure lumen diameter and intra-balloon 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 only available balloon that was 8 cm in length. 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 or

greater in height, and an 8 cm length balloon was used for those less than 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 (EGJ). 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 to 20 seconds. 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 mmHg. 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 mmHg[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. [10,11,17]

Endoscopic and Histologic Assessment

The esophageal appearance was prospectively recorded by the performing physician prior to FLIP using a validated esophageal endoscopic reference scale[13]. Presence of 1) edema, white plaques and/or linear furrows was categorized as inflammatory endoscopic features and 2) 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 H&E 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 to 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 less than 35 μm lamina propria thickness (a superficial region that normally appears compacted), or samples where technical (crush) artifact impairs scoring[14].

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[15].

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) low weighted filter to identify the location of the EGJ and to assess degree of secondary peristalsis. To subtract the EGJ, electrodes spanning 1 to 2 cm proximal to the EGJ (for the 8 and 16 cm catheter respectively) and distal were excluded from next steps in analysis. Secondary peristalsis was categorized as mild, moderate or severe based on a semi-quantitative frequency of antegrade or retrograde contraction. Severe was defined as >= 5 contractions in a 30 second period resulting in a decrease in the lumen diameter by >= 5mm for >= 25% of inflation time. Moderate was defined as >= 2 contraction in a 30 second window for >=25% of inflation time. Mild was any lesser degree of contraction.

To determine distensibility of the esophageal lumen, raw FLIP data was downloaded to statistical software and filtered for analysis. Data was filtered by the following means: 1) raw data was aggregated to every 5 seconds and 2) to mitigate the effect of esophageal peristalsis and respiration on intrabag pressure and lumen diameter, 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 identified. The primary outcome was then determined by the minimal diameter at a mean intrabag pressure of 40 mmHg (distensibility). Data was filtered and analyzed with STATA (College Station, TX).

Data Analysis—SAS 9.4 (SAS Institute Inc. Cary, NC) was the statistical software used for data analysis. The outcome variable, distensibility was tested for normality. Mean and standard error were used to summarize the outcome. Other continuous and categorical variables are summarized using mean and standard deviation and percent 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 male) and 88 EoE pediatric subjects (68 male) were enrolled. Median ages are 11.1 (3.0 to 17.8) for non-EoE and 12.0 (4.2 to 18.6) for EoE. (Table 1) The primary indication for endoscopy in the non-EoE controls and the final diagnosis post endoscopy is depicted in Table 2 and Supplementary Table 2.

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 to 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 5 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 post procedure pain in this cohort. The FLIP measurement added 4 minutes 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, Supplemental Figure 1A–1C) Multiple linear regression analyses indicated 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, Supplemental Figure 1D–1F). While age did not have significant correlation with distensibility in the EoE population, age was maintained as a confounding variable in analysis.

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 cohort [(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 to non-EoE controls—Unadjusted comparison between EoE and non-EoE controls demonstrates a significant decrease in distensibility in EoE subjects [14.95 mm +/− 2.66 vs 17.24 mm +/− 2.56, $p<0.0001$ 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 to non-EoE controls (mean distensibility in non-EoE vs EoE [17.13 mm (+/− SEM 0.229) vs 14.65 mm (+/− SEM 0.229)), $p < 0.0001$]) (Figure 2B). Distensibility increased by 0.33 mm per one 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 to those EoE subjects with inactive inflammation (eos < 5 eos/hpf) [mean distensibility 14.09 mm (+/− SEM 0.37) vs 16.07 (+/− SEM 0.42), p-value 0.0007] (Figure 3A). Subjects with intermediate inflammation (5 to 15 eos/hpf) also had

intermediate distensibility [mean distensibility 14.81 mm (+/− SEM 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).

Discussion

Using the novel endoscopic tool, FLIP, we show for the first time that pediatric esophageal distensibility is significantly decreased in children with significantly active EoE compared to 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 to those EoE patients without these symptoms. Our data are particularly interesting since they indicate that this device can be used successfully in children and provide a reliable and 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 the that 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 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 versus 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 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[16].

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 to age matched controls. Alternatively, it could reflect an underlying fibrostenotic phenotype that assumes a less distensible pattern with or without treatment.

Decreased esophageal distensibility was associated with 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 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 histologic assessment. Our results suggest 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 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. While 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, [17] Until this observed trend can be directly studied, we recommend that when following patients longitudinally that 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 less than 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 is analyzed. (17) In the 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 contract 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 2 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 over 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 PPI. Our control group may have included patients with PPI responsive esophageal eosinophilia, although to the best of our knowledge that is not the case (Table 2 and Supplementary Table 1). Second, while 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. While 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. While 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; 1) controlling inflammation may improve distensibility and 2) 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 eosinophilic esophagitis 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

EoE	Eosinophilic Esophagitis
FLIP	endoluminal functional lumen imaging probe
eos/hpf	eosinophils per high power filed

EGJ esophagogastric junction

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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 population
- Esophageal distensibility is decreased in pediatric EoE patients
- There is decreased distensibility in patients with increased disease activity and lamina propria fibrosis

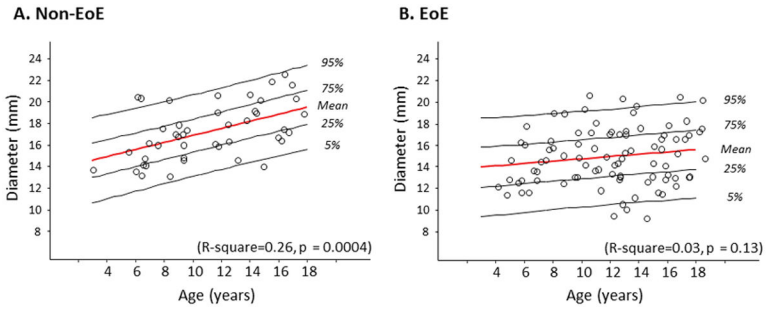

Figure 1.

Regression line and prediction intervals for distensibility of the esophageal lumen across age in A) non-EoE controls and B) EoE subjects. Distensibility significantly increases in controls but not in EoE subjects.

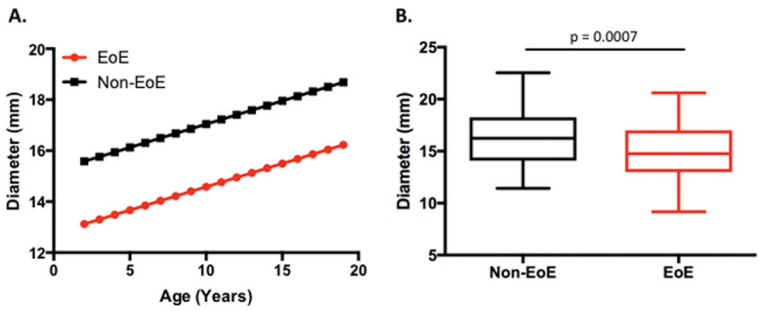

Figure 2.

Predicted distensibility by age given EoE status using a prediction model without interaction terms (best fit). Diameter increases by 0.33 mm per one year older. Adjusting for age distensibility is reduced in EoE as compared to non-EoE by 26%.(A) Box-whisker plot for distensibility in EoE as compared to non-EoE controls. (B)

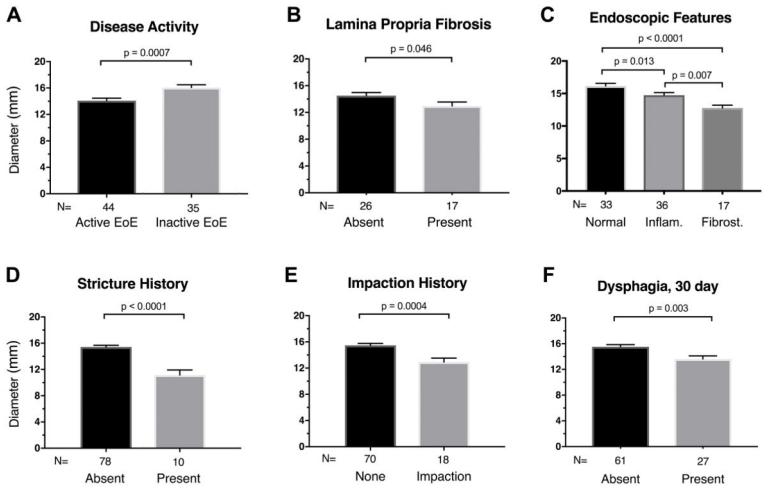

Figure 3.

Distensibility in EoE subgroups. Mean distensibility is decreased in EoE subjects with; (A) active inflammation (>15 eos/hpf) compared to those with inactive inflammation (<5 eos/hpf); (B) lamina propria fibrosis; (C) endoscopic features of fibrostenosis; (D) recent dysphagia; (E) history of food impaction; (F) history of stricture. Error bars represent SEM. All comparisons were adjusted for age and catheter type.

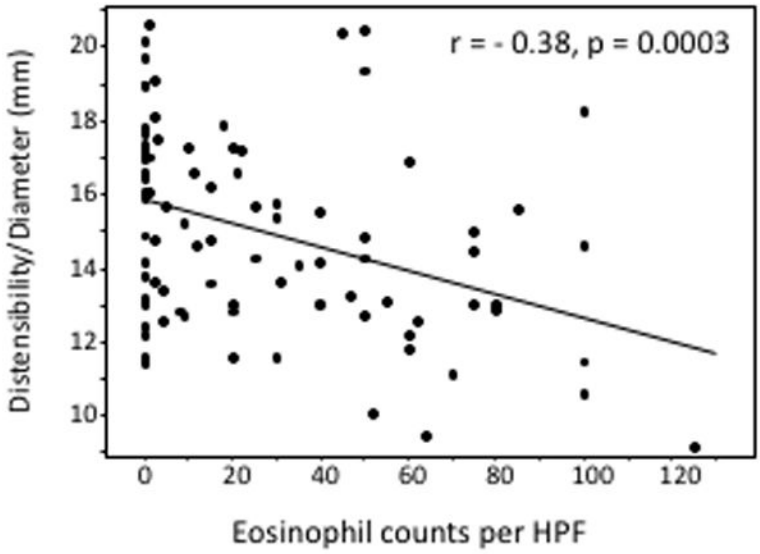

Figure 4.

Lumen diameter versus peak eosinophils per high power fields for all 88 EoE patients. There is a moderate but significant negative correlation between distensibility and peak eosinophil count in EoE subjects.

Table 1

Patient characteristics.

	Non-EoE (44)	EoE (88)	P-values
Age (mean ± SD)	11.06 ± 3.98	12.00 ± 3.93	0.20
Male	22 (50.0%)	68 (77.3%)	0.003
Height, cm (mean ± SD)	143.7 ± 24.1	148.31 ± 22.65	0.28
Weight, kg (mean ± SD)	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%)	0.0007
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 ± SD,[range])	0.0 (0, 0 to 0)	27.9 (31.6, 0 – 125)	<0.001
Catheter length - 80mm	28 (63.6%)	44 (50.0%)	0.19
Catheter length - 160mm	16 (36.4%)	44 (50.0%)	

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

PPI – proton pump inhibitor, Eos/hpf – eosinophils per high power field

Table 2

Non-EoE Control Clinical Information

Primary Presenting Symptom	Number
Abdominal Pain	21
Dysphagia/Difficulty swallowing	10
Heartburn or reflux	8
Diarrhea	2
Failure to thrive/Weight loss	2
Vomiting	2
Final Diagnosis	**Number**
Functional Abdominal Pain	8
Non-erosive GERD	7
Dyspepsia	4
Lactose Intolerance	3
Other *	6
Resolved	9
No GI follow up	7

*Other included celiac disease (1), non-celiac gluten sensitivity (1), fool allergies without GI diagnosis (1), sigmoid volvulus (1) and FTT due to inadequate caloric intake (2)