The Slender Esophagus: Unrecognized Esophageal Narrowing in Eosinophilic Esophagitis

Kristle L. Lynch, MD[1], Alain J. Benitez, MD[2], Bridget Godwin, MD[2], Jeremy Klein, BS[2], Deepika Savant, MD[3], Benjamin J. Wilkins, MD PhD[4], Calies Menard-Katcher, MD[5], Craig Gluckman, MD[1], Gary W. Falk, MD, MS[1] and Amanda Muir, MD[2]

INTRODUCTION: **Inflammation in eosinophilic esophagitis (EoE) often leads to esophageal strictures. Evaluating esophageal narrowing is clinically challenging. We evaluated esophageal distensibility as related to disease activity, fibrosis, and dysphagia.**

METHODS: **Adult patients with and without EoE underwent endoscopy and distensibility measurements. Histology, distensibility, and symptoms were analyzed.**

RESULTS: **Patients with EoE had significantly lower distensibilities than controls. We found a cohort with esophageal diameter under 15 mm despite lack of dysphagia.**

DISCUSSION: **This study raises concern that current assessments of fibrostenosis are suboptimal. We describe a cohort with unrecognized slender esophagus that were identified through impedance planimetry measurements. This tool provides additional information beyond symptomatic, histologic, and endoscopic assessments.**

KEY WORDS: dysphagia; eosinophilic esophagitis; stricture

Clinical and Translational Gastroenterology 2023;14:e00564. https://doi.org/10.14309/ctg.0000000000000564

INTRODUCTION

Eosinophilic esophagitis (EoE) is an allergic inflammatory condition characterized by esophageal infiltration of eosinophils. Natural history studies suggest that unchecked inflammation ultimately leads to fibrostenotic disease (1). However, before the onset of frank strictures, esophageal narrowing is challenging to assess symptomatically due to lifestyle changes such as food avoidance and prolonged eating. Determining the degree of fibrostenosis is challenging with esophagogastroduodenoscopy, radiography, and biopsies alone, which allow for limited sampling and assessment of esophageal diameter (2). Understanding esophageal stiffness, narrowing, and distensibility requires further modalities.

The endolumenal functional lumen imaging probe (FLIP) provides novel information on esophageal distensibility. Thus far, limited studies of adult patients reveal that patients with EoE have lower esophageal distensibility than control patients (3–5). However, the relationship between distensibility and disease activity may vary by age. We therefore sought to evaluate the relationship between histologic, endoscopic, and symptomatic findings and esophageal distensibility in adult patients with EoE and to determine the utility of EndoFLIP in distinguishing "slender" esophagus missed on routine endoscopy.

METHODS

Adult patients with EoE were prospectively recruited at the Hospital of the University of Pennsylvania. Patients were excluded if they had any anatomic esophageal abnormality unrelated to EoE, a history of chest radiation, esophageal surgery, motility disorder, or inflammatory bowel disease. Symptom assessment was performed on the day of the endoscopy. Control patients with normal esophageal biopsies were included; most of these patients underwent endoscopy for reflux, dyspepsia, nausea, and vomiting. This study was approved by our center's institutional review board. All subjects provided informed consent.

The FLIP EF-322 catheter (Medtronic, Fridley, MN) was used in this study. The probe was placed transorally and passed to the esophagogastric junction, as described by Nicodeme et al (4). Distensibility plateau was defined by the minimal esophageal body diameter at maximum esophageal distension at an intrabag pressure of 40 mm Hg using methods described by Menard-Katcher et al (5). Standard clinical practice biopsies were obtained after FLIP measurements, and eosinophil counts were assessed by pathologists. Esophageal biopsies were analyzed using the lamina propria (LP) scores from the EoE-histology scoring system (6). A

[1]Division of Gastroenterology and Hepatology, The University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA; [2]Division of Gastroenterology and Hepatology, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA; [3]Department of Pathology and Laboratory Medicine, The University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA; [4]Department of Pathology and Laboratory Medicine, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA; [5]Section of Pediatric Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, University of Colorado School of Medicine, Digestive Health Institute, Children's Hospital Colorado, Aurora, Colorado, USA. **Correspondence:** Kristle L. Lynch, MD. E-mail: Kristle.Lynch@pennmedicine.upenn.edu.

Received August 15, 2022; accepted December 27, 2022; published online January 5, 2023

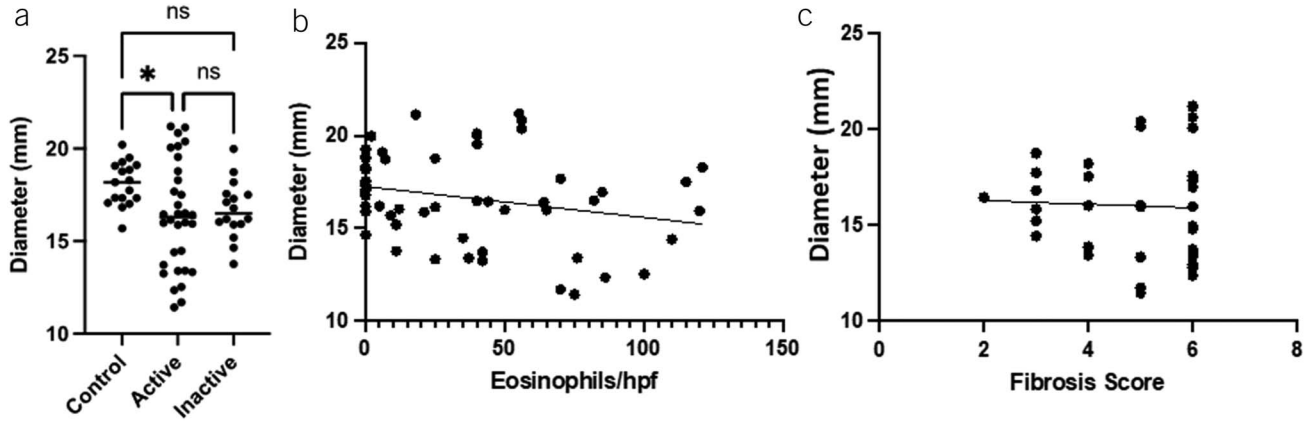

Figure 1. (**a**) Comparison of distensibility measurements in patients with eosinophilic esophagitis (EoE) and control patients. Distensibility is significantly lower in patients with EoE, but similar between active and inactive patients with EoE. $^*P < 0.05$. (**b**) Correlation of distensibility and eosinophil count, $R^2 = -0.06$, $P = 0.0502$. (**c**) Correlation of distensibility and fibrosis score, $R^2 = 0.0017$, $P = 0.8103$.

score of "not applicable/evaluable" was reported for samples containing <35 μm LP thickness or samples where technical artifact impaired scoring.

Data are presented as mean values ± SEMs or mean values ± SDs and were analyzed by using the 2-tailed Student *t* test or ANOVA or the χ^2 test, where applicable. A *P* value of less than 0.05 was considered significant. Data were analyzed with the software package Prism (GraphPad Software, La Jolla, CA). All authors had access to the study data and reviewed and approved the final manuscript.

RESULTS

Forty-eight adult patients with EoE and 17 control patients were enrolled in this study. Patients were predominantly White (92%), male (56%), and younger than 50 years (88%). Both active and inactive patients with EoE had a significantly lower distensibility index compared with control patients ($P < 0.05$ for active vs control and inactive vs control) (Figure 1a). Similar to the findings of Nicodeme et al, patients with active EoE (defined as greater than 15 eosinophils per high-power field) had similar distensibility measurements as inactive patients (4). Distensibility index did not correlate with eosinophil counts in patients with EoE ($R^2 = -0.06$, $P = 0.0502$) (Figure 1b and c). Patients with a history of stricture requiring dilation did not have significantly different distensibility compared with those without, although there was an overall small population with previous dilation (Figure 2). Strikingly, patients with a history of food impaction requiring endoscopic removal or symptoms of dysphagia in the preceding 30 days did not have differences in their distensibility compared with those without these factors. We eliminated patients with any critical narrowing (<10 mm) requiring dilation during the procedure.

In total, 13 of the 48 patients with EoE had an esophageal diameter less than 15 mm. The diameter of active patients with EoE ranged from 11.43 to 21.2 mm while the diameter of inactive patients with EoE ranged from 13.77 to 19.98 mm (Figure 1a). Of the patients with a diameter <15 mm, 6 had no dysphagia, 6 had no prior food impaction, and 11 had no prior stricture (Table 1). Comparison of the populations did not show any significant differences between the population with >15 mm esophagus and those with <15 mm save for disease activity, although the presence of rings and trended toward significance. Taken together, these results demonstrate a population without known complications, symptoms, or endoscopic findings that has a narrowed esophagus.

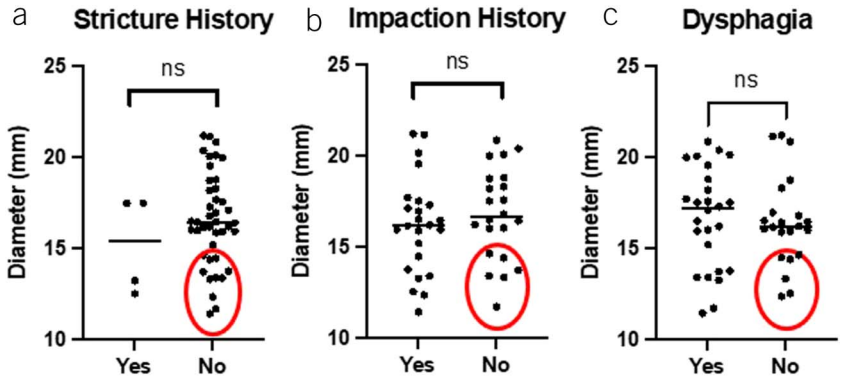

Figure 2. Distensibility of patients with stricture, impaction, and dysphagia. (**a**) Distensibility of patients with a history of stricture requiring dilation (mean distensibility 15.2 mm) and those without (mean 16.59 mm), $P = 0.31$. (**b**) Patients with a history of impaction requiring endoscopic retrieval (mean distensibility 16.17 mm) compared with those without (mean distensibility 16.79 mm), $P = 0.4175$. (**c**) Patients with a history of dysphagia in the last 30 days (mean distensibility 16.68 mm) compared with those without (mean distensibility 16.23 mm), $P = 0.486$. Red circles indicate patients with esophageal caliber <15 mm who have no history of stricture, history of impaction, or dysphagia.

Table 1. Characteristics of patients with narrow caliber esophagus

	<15 mm diameter (n = 13)	>15 mm diameter (n = 35)	*P* value
Male, n (%)	8 (61.5)	24 (68.5)	0.64
Dysphagia	7 (53.8)	24 (68.5)	0.34
Impaction	7 (53.8)	21 (60)	0.7
Abdominal pain	1 (7)	4 (11)	0.7
Heartburn	4 (30.7)	13 (37)	0.68
Stricture	2 (15)	4 (11)	0.7
Eosinophil count <15, n (%)	2 (15)	18 (51)	**0.02**
Rings (%)	81% (9/11)	46% (12/25)	0.058
Exudates (%)	36% (4/11)	44% (11/25)	0.66
Furrows (%)	58% (7/12)	37% (13/35)	0.2
Edema (%)	80% (8/10)	79% (19/24)	0.95
Age at diagnosis	30.1 (10.1)	34 (15)	0.46

P value <.05 is bolded.

DISCUSSION

In EoE, dysphagia symptoms, histology, and endoscopic appearance do not necessarily shed light on true diameter. Our data suggest a group of patients with a slender esophagus (diameter ranging from 10 to 15 mm) with no histologic signs of fibrosis and no frank dysphagia. Using FLIP, we identified patients with a previously unrecognized slender esophagus and targeted these patients for more aggressive management and dilation.

This study confirms prior findings in both adult and pediatric populations showing that esophageal distensibility is decreased in EoE. Furthermore, it demonstrates that the absence of disease activity does not necessarily improve distensibility in the adult population; a finding that stands in striking contrast to the pediatric population (5,7,8). A recent EoE disease severity index has been published, which focuses on symptoms, eosinophil count, endoscopic findings, the presence of LP, and the ability to pass a standard adult upper endoscope (9). Furthermore, it takes complications including emergent food impactions and a history of dilation into account. Our data reveal an EoE subgroup with an abnormal esophageal diameter that lacks obvious dysphagia, narrowing, inflammation, or complications. In addition, patients with a slender esophagus may be clinically indistinguishable from patients in deep remission due to careful food selection and behavioral adjustments. Thus, it may be challenging to assign a true disease severity score in these cases without the use of advanced technology.

One new finding from our study was that the degree of LP fibrosis as scored by extent and grade showed no relationship with distensibility. While previous reports determined that the rates of adequate LP sampling occur in approximately 50% endoscopies with biopsy, if present, it was believed to be a reliable marker of remodeling in the subepithelium (2,5). However, our results highlight that there is little difference in distensibility based on the severity of LP fibrosis. Therefore, relying solely on LP fibrosis, even when adequately sampled, may not be sufficient to evaluate subepithelial remodeling or adequately characterize the EoE phenotype.

This study highlights the dichotomy between dysphagia assessment and esophageal diameter. Simple symptom assessment does not capture the status of the esophagus. An in-depth understanding of symptoms with interrogation of eating habits is required, and measurements through impedance planimetry may provide a more complete assessment. In this study, we used FLIP to elucidate a novel cohort of patients with EoE with a slender esophagus that may be overlooked. These patients may benefit from dilation and optimization of medical management to improve both quality of life and alter remodeling.

CONFLICTS OF INTEREST

Guarantor of the article: Kristle L. Lynch, MD.

Specific author contributions: K.L.L. was involved in study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript and critical revision of the manuscript. A.J.B. was involved in the study concept and design, drafting the manuscript, and critical revision of the manuscript. B.G. was involved in study concept and design, analysis and interpretation of data, and critical revision of the manuscript. J.K. was involved in acquisition and interpretation of data, and critical revision of the manuscript. D.S. was involved in acquisition of data, and critical revision of the manuscript. B.W. was involved in acquisition of data, and critical revision of the manuscript. C.M.-K. was involved in study concept and design, analysis and interpretation of data, and critical revision of the manuscript. C.G. was involved in acquisition and interpretation of data, and critical revision of the manuscript. G.W.F. was involved in study concept and design and critical revision of the manuscript. A.B. was involved in study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript and critical revision of the manuscript.

Financial support: K.L.L. and A.M. supported by Donald Castell American Gastroenterological Association Grant funding. A.M. and C.M.-K. supported by Foundation for the National Institutes of Health (R21TR003039-02).

Potential competing interests: G.W.F. is a consultant for Adare/Ellodi, Allakos, Celgene/Bristol Myers Squibb, Nexstone, Lucid, Regeneron/Sanofi, and Upstream Bio and has research grant support from Adare/Ellodi, Allakos, Arena/Pfizer, Celgene/Bristol Myers Squibb, Lucid, Regeneron/Sanofi, and Shire/Takeda. K.L.L. is a consultant for Medtronic, LUCID, and Takeda. A.M.B. receives research funding from Morphic and Allakos and serves as a consultant for Nexstone and Medtronic. B.G. is currently an employee of Janssen Pharmaceuticals but was not during thewriting of this manuscript. No external companies had any part in the study design, data interpretation, data analysis, nor the decision to submit the article for publication. To the best of our knowledge, no conflict of interest, financial or other, exists.

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(6):1230–6.e62.
2. Wang J, Park JY, Huang R, et al. Obtaining adequate lamina propria for subepithelial fibrosis evaluation in pediatric eosinophilic esophagitis. Gastrointest Endosc 2018;87(5):1207–14.e3.
3. Hassan M, Aceves S, Dohil R, et al. Esophageal compliance quantifies epithelial remodeling in pediatric patients with eosinophilic esophagitis. J Pediatr Gastroenterol Nutr 2019;68(4):559–65.
4. Nicodème 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(9):1101–7.e1.

5. Menard-Katcher C, Benitez AJ, Pan Z, et al. Influence of age and eosinophilic esophagitis on esophageal distensibility in a pediatric cohort. Am J Gastroenterol 2017;112(9):1466–73.
6. 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 2017;30(3):1–8.
7. Muir AB, Ackerman SJ, Pan Z, et al. Esophageal remodeling in eosinophilic esophagitis: Relationships to luminal captured biomarkers of inflammation and periostin. J Allergy Clin Immunol 2022;150(3): 649–56.e5.
8. 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(12):1844–53.
9. Dellon ES, Khoury P, Muir AB, et al. A clinical severity index for eosinophilic esophagitis: Development, consensus, and future directions. J Allergy Clin Immunol 2022;150(1):33–47.