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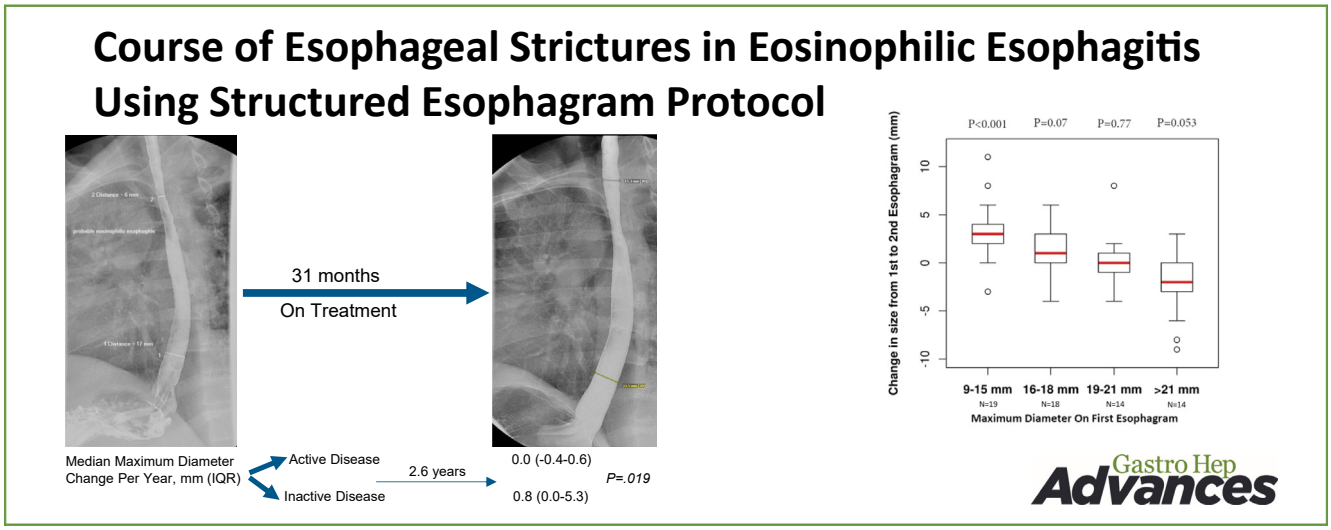
ORIGINAL RESEARCH—CLINICAL

Course of Esophageal Strictures in Eosinophilic Esophagitis Using Structured Esophagram Protocol

Diana L. Snyder,[1] Jeffrey A. Alexander,[1] Karthik Ravi,[1] Jeff L. Fidler,[2] and David A. Katzka[3]

From the [1]Division of Gastroenterology, Mayo Clinic Rochester, Rochester, Minnesota; [2]Department of Radiology, Mayo Clinic Rochester, Rochester, Minnesota; and [3]Division of Gastroenterology, Columbia University, New York, New York



BACKGROUND AND AIMS: A key unknown in eosinophilic esophagitis (EoE) is the long-term course of esophageal stenosis. Our aim was to evaluate the course of esophageal strictures using structured serial esophagrams and determine predictors of diameter improvement in patients with EoE. **METHODS:** This was a retrospective study of 78 EoE patients who completed 2 structured esophagrams at an academic tertiary referral center between 2003 and 2021. Maximum and minimum esophageal diameters were measured during esophagram using a standardized protocol to reduce measurement errors. **RESULTS:** The median age at first esophagram was 36.2 (12.9–64.3) years; 60.3% of patients were male; 41 patients had active EoE; and 9 were inactive. Of the patients, 39.7% had allergic rhinitis, asthma (32.1%), and atopic dermatitis (7.7%). Medical therapies at second esophagram and esophagogastroduodenoscopy included proton pump inhibitors (39.5%), swallowed topical steroids (31.6%), diet elimination (13.2%), biologic therapies (1.3%), and clinical trial medications (1.3%). Median maximum diameter significantly increased by 1.0 mm (Q1: −1.0 mm, Q3: 3.0 mm) ($P = .034$), independent of dilation ($P = .744$). Increase was most profound in patients starting in the lowest maximum diameter group (9–15 mm) with median increase of 3.0 mm. For patients in disease remission at the second esophagram, there was a significant increase in maximum diameter per year compared to active disease at 0.8 mm (Q1: 0.0 mm, Q3: 5.3 mm) and 0.0 mm (Q1: −0.4 mm, Q3: 0.6 mm) respectively ($P = .019$). **CONCLUSION:** Long-term improvement in esophageal strictures in patients with EoE may occur but is modest and likely occurs over years. Progression also appears to be minimal. Continuous medical treatment may reduce the rate of stricture recurrence and may improve stricture diameter over time.

Keywords: Eosinophilic Esophagitis; Esophagram; Esophageal Stricture

Introduction

Almost all adult patients with eosinophilic esophagitis (EoE) present with dysphagia and/or food impaction.[1] Similarly, a lack of treatment or diagnostic delay leads to a higher prevalence of fibrotic or fibroinflammatory strictures in over 85% of patients with EoE after 20 years.[2]

Abbreviations used in this paper: **EoE, eosinophilic esophagitis.**

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As a result, one of the key goals of long-term medical therapy for EoE is the prevention or reversal of fibroinflammatory strictures.

The fibrogenic pathway in EoE is mediated by multiple cytokines and cells. These include eosinophil and immune cell production of Eotaxin-3 and IL-13 activation fibroblasts to secrete extracellular matrix.[3] Topical steroids may be effective in attenuating pathways of inflammation and fibrosis in EoE animal models and human tissue. Several lines of data support this. For example, use of topical steroids can reduce markers of lamina propria fibrosis in patients with EoE.[4] Steroids may also reduce the occurrence of food impaction[5] and decrease the need for esophageal dilation suggesting a therapeutic increase in the esophageal lumen diameter. Data on this is limited, and further study is needed to understand the effects of steroids on the complex process of esophageal remodeling.[6]

Although these data are encouraging for medical therapy of esophageal strictures, several important issues remain unresolved. For example, there is no reliable test that assesses what proportion of an esophageal stricture is fibrotic or inflammatory. Although it is hoped that lamina propria fibrosis mirrors esophageal wall scarring,[7,8] this has not been convincingly demonstrated. As a result, an increase in the size of the esophageal lumen may reflect improvement in inflammation acutely, as likely as fibrosis, over the course of several months of therapy.[9] Partial resolution of fibrosis in chronic inflammatory diseases as a general model of disease and therapeutic modulation of chronic fibrotic change in disease has been demonstrated elsewhere in the gastrointestinal tract and human body including skin, kidney, and liver.[10] However, in those diseases where there is resorption of collagen and stabilization and/or improvement in fibrosis, it requires years to occur. For example, studies have demonstrated that in patients with hepatic cirrhosis, favorable changes in gross liver architecture require years before occurrence. In a series of trials for hepatitis C virus and hepatitis B virus, there was a range of reversal in fibrosis at 0%–88%, but notably only after a minimum of 16 months of antiviral treatment.[10] For 2 trials lasting up to 18 months, reversal occurred in only 0%–27% of patients. Furthermore, data on infectious hepatitis is the most favorable and fastest when compared to other forms of hepatic cirrhosis for reversal of this process.

There thus remains a controversy in the medical treatment of esophageal strictures in patients with EoE. Without the ability to grossly evaluate the esophageal wall and discern inflammation from fibrosis, translation of histologic and animal data supporting attenuation of fibrosis into resolution of scarring cannot be applied with certainty. One method that may be helpful in addressing this controversy is the use of a structured barium esophageal measuring fixed esophageal diameter.[9,11] At our institution, this is the long-term standard for evaluation of the esophageal lumen in EoE and therefore provides a unique data set to analyze changes in diameter over the period of years that may require remodeling to occur. In this study using structured serial esophagrams, the course of esophageal strictures and predictors of improvement were assessed longitudinally in patients with EoE.

Methods

This was a retrospective study of 78 EoE patients (>12 years) who completed 2 structured esophagrams at an academic tertiary referral center between 2003 and 2021. EoE was defined by consensus criteria with ≥15 eosinophils per high power field on esophageal biopsies in the absence of secondary causes of esophageal eosinophilia.[12] The methods for performing a structured esophagram were previously reported[11] (Figure 1). Static strictures and esophageal diameter were confirmed on multiple images to eliminate the possibility of esophageal narrowing due to motility, as per routine radiologic technique in esophagography.

Baseline demographics, medication use, and endoscopic data with histology were obtained through chart review. In our institution, a baseline esophagram is routinely obtained in all patients with EoE and repeated at least 1 year after treatment and periodically as a means of assessing possible progression of esophageal stricture formation. Esophageal diameter was compared between each patient's first and second esophagram. This is performed in addition to endoscopy and esophageal biopsies during follow-up; though not necessarily at the same time. Barium tablets are not routinely used in our EoE patients due to the risk of impaction in patients with esophageal stricture diameters <0.5 inches, the size of the tablet.

Patients included had an esophagogastroduodenoscopy within 3 months of the second esophagram on stable medical therapy. EoE was considered active by >15 eosinophils/high power field or lack of therapy.[1] Change in esophageal diameter between the first and second esophagram was analyzed using the Wilcoxon signed rank test and reported as median, 25th percentile (Q1), and 75th percentile (Q3) values. Four subgroups were defined by initial maximum esophageal diameter to assess the effect of baseline severity on change: 9–15 (n = 19), 16–18 (n = 18), 18–21 (n = 14), and >21 mm (n = 14). Kruskal-Wallis testing was used to analyze differences in diameter change based on starting diameter.

Results

The median age at first esophagram was 36.2 (12.9–64.3) years, and 60.3% of patients were male. At first esophagram, 41 patients had known active EoE and 9 were inactive. Allergic rhinitis (39.7%), asthma (32.1%), and atopic dermatitis (7.7%) were present in patients. Food impaction, defined as food held for more than 5 minutes or requiring an emergency department evaluation, occurred in 59.7% of patients. Medical therapies at the time of the second esophagram and esophagogastroduodenoscopy included proton pump inhibitors (39.5%), swallowed topical steroids (31.6%), diet elimination (13.2%), biologic therapies (1.3%), and clinical trial medications (1.3%). Eleven (14.1%) and 35 patients (44.9%) had a dilation before the first or between esophagrams, respectively. For patients with dilation between esophagrams, median time

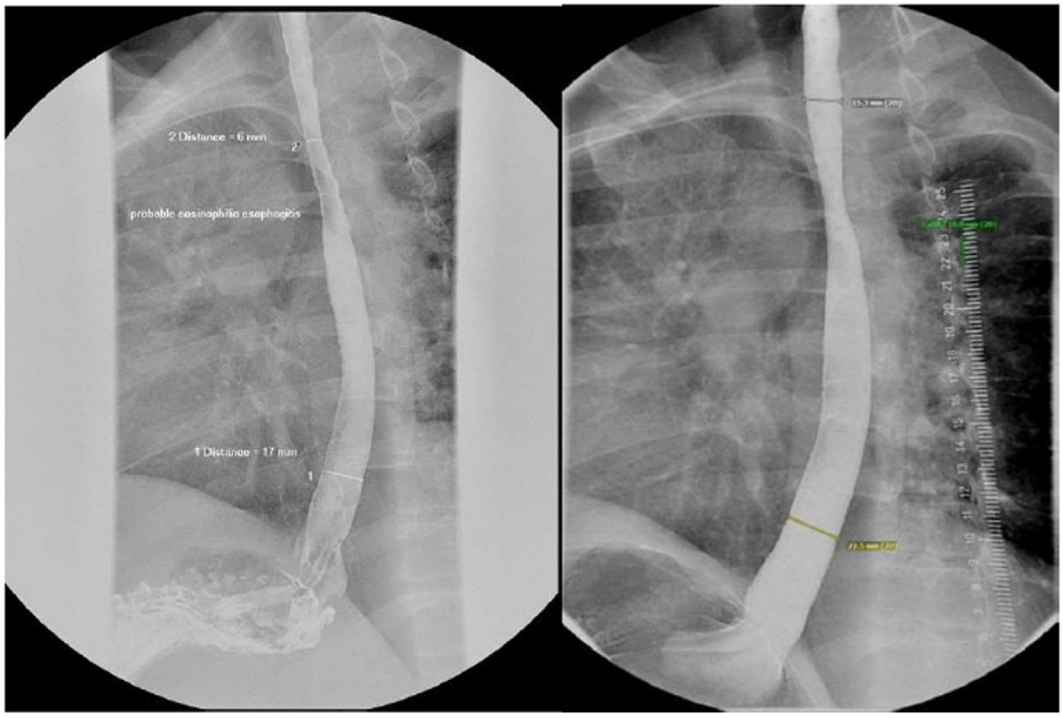

Figure 1. Example of patient with an increase in maximum esophageal diameter between esophagrams 1 and 2. Time between esophagrams was 31 months. The patient had active disease at the time of the first esophagram and was in histologic remission at the time of the second esophagram. The maximum and minimum esophageal diameters were measured on images obtained during rapid swallowing in the right anterior oblique recumbent position. Measurements are calibrated to a reference to prevent magnification errors and facilitate reproducible methods between radiologists. Maximum diameter of initial esophagram is 17 mm, and 22.5 mm in follow-up esophagram.

from last dilation to second esophagram was 15 months (range 0–82). Dilation was not performed in 15 (19.2%) patients and only occurred after the second esophagram in 19 (24.4%). There was no difference in the number of dilations per year for the years of EoE diagnosis 1998–2011 and 2012–2021 ($P = .119$).

There was a median of 2.6 years (range 0.1–12.4) between esophagrams (Table). Median maximum diameter increased by 1.0 mm (Q1: −1.0 mm, Q3: 3.0 mm) ($P = .034$), independent of dilation ($P = .744$). Median maximum change in diameter per year increased by 0.4 mm (Q1: −0.4 mm, Q3: 1.3 mm) ($P = .010$). Change in maximum diameter did not differ on (n = 47) or off medical therapy (n = 27), respectively [1.0 mm (Q1: −1.0 mm, Q3: 3.0 mm) and 1.0 mm (Q1: 0.0 mm, Q3: 2.0 mm), $P = .640$]. In contrast, patients with inactive disease (n = 15) had an increase in maximum diameter per year compared to those who had active disease (n = 33) at 0.8 mm (Q1: 0.0 mm, Q3: 5.3 mm) and 0.0 mm (Q1: −0.4 mm, Q3: 0.6 mm), respectively ($P = .019$). There was no difference in median maximum diameter change comparing patients taking swallowed topical steroids with proton pump inhibitors [0.0 mm (Q1: −3.0 mm, Q3: 3.0 mm) vs 0.5 mm (Q1: −1.0 mm, Q3: 3.0 mm), $P = .949$]. The increase was greatest in the 9–15 mm group with an increase of [3.0 mm (Q1: 2.0 mm, Q3: 4.0 mm, $P < .001$] (Figure 2). In the >21 mm group, a nonsignificant trend toward further narrowing occurred [−2.0 mm (Q1: −3.0 mm, Q3: 0.0 mm), $P = .053$]. There was a difference in change in diameter comparing the 9–15 mm to the 19–21 mm and >21 mm groups ($P = .004$ and $P \leq .001$, respectively). Minimum diameter changes were also analyzed. There was no change in minimum diameter between esophagrams ($P = .277$). There was no difference in minimum diameter for presence or absence of medical therapy during second esophagram at 1.0 mm (Q1: 0.0 mm, Q3: 3.0 mm) and −0.5 mm (Q1: −3.0 mm, Q3: 0.0 mm) respectively ($P = .082$). There was a trend toward increased minimum diameter per year between esophagrams by 0.5 mm (Q1: 0.0 mm, Q3: 1.3 mm) for patients on therapy compared to those who were not, with a median of −0.1 mm (Q1: −0.7 mm and 0.0 mm) ($P = .058$). Remission was not associated with change in minimum diameter overall ($P = .461$) or per year ($P = .180$).

Discussion

This study followed patients for up to 12 years with serial measurements of esophageal diameter. For completeness, we measured both the maximal and minimal esophageal diameter. Although it would seem a bolus is most likely to obstruct at the level of minimum diameter,

Table. Esophagram Measurements of Change in Maximum and Minimum Diameter Classified by Dilation, Medical Therapy, and Disease Activity

Total median change	Total (n = 78)	*P* value	No dilation (n = 43)	Dilation (n = 35)	*P* value	Off medical therapy (n = 27)	On medical Therapy (n = 47)	*P* value	Active disease (n = 33)	Remission (n = 15)	*P* value
Median years between esophagrams (range)	2.6 (0.1–12.4)		2.7 (0.1–11.6)	2.4 (0.1–12.4)							
Median maximum diameter change, mm (IQR)	1.0 (−1.0 to 3)	.034	1.0 (−1.0 to 2.5)	1.0 (0.0–3.0)	.744	1.0 (0.0–2.0)	1.0 (−1.0 to 3.0)	.640	0.0 (−1.0 to 2.0)	2.0 (0.0–3.0)	.180
Median maximum diameter change per year, mm (IQR)	0.4 (−0.4 to 1.3)	.010	0.3 (−0.4 to 1.5)	0.4 (0.0–1.3)	.961	0.4 (0.0–0.9)	0.3 (−0.4 to 1.7)	.804	0.0 (−0.4 to 0.6)	0.8 (0.0–5.3)	.019
Median Minimum diameter change, mm (IQR)	0.0 (−1.5 to 2.0)	.277	0.0 (−2.0 to 2.0)	1.0 (−1.0 to 3.0)	.317	−0.5 (−3.0 to 0.0)	1.0 (0.0–3.0)	.082	0.0 (−2.0 to 3.0)	2.0 (0.0–3.0)	.461
Median minimum diameter change per year, mm (IQR)	0.0 (−0.5 to 1.1)	.059	0.0 (−0.7 to 0.9)	0.4 (−0.3 to 1.5)	.249	−0.1 (−0.7 to 0.0)	0.5 (0.0–1.3)	.058	0.0 (−0.6 to 1.1)	0.8 (0.0–5.3)	.181

IQR, interquartile range, 25th–75th percentile; mm, millimeters.

the potential pattern of stricture resolution is unclear with regards to which measure(s) of esophageal lumen improve over time; hence, measurement of both was completed. The results demonstrated that maximum esophageal diameter increased over time in those with inactive disease, independent of dilation and medical therapy. Nevertheless, the change in stricture diameter was modest for most patients with no significant change in many of the meaningful endpoints. The EoE group that appeared to benefit most were those patients with the smallest starting diameter, although the overall diameter change was small at 3 mm. On the other hand, there was no overall significant progression of esophageal narrowing in any of the groups. These findings occurred independently of the use of dilation.

In fact, the only factor that favorably influenced the course of esophageal diameter was remission of disease and not dilation. Whether this therapeutic effect was on inflammation, fibrosis, or both is unknown. It makes intuitive sense that patients in the small-diameter group would have the greatest component of inflammation in addition to fibrosis, thereby predicting the maximal anti-inflammatory effect. This finding is morphologically similar to patients with narrow-diameter long strictures associated with Crohn's disease (string sign), another chronic inflammatory disease of the gut in which a significant part of the intestinal wall thickening is due to inflammation and fibrosis distinguished on magnetic resonance enterography.[13] The string sign in Crohn's disease may well be an equivalent of the small-caliber esophagus in EoE. It may also not be surprising that in a follow-up mean of only 2.2 years, there was a lack of a formidable change in esophageal diameter in our study. In patients with Crohn's disease who have undergone stricturoplasty, recurrent fibrosis may be diminished only after a period of 2 years.[14]

One important question raised by this study is whether this data warrants continued medical therapy for patients with EoE. Although we saw no significant change in esophageal diameter between those with medical therapy vs not on therapy, one may look at this as a positive sign that there was no progression. Furthermore, there was a significant increase in esophageal diameter for patients with disease in remission on follow-up. Together, we still find this supportive of continuing medical therapy for these patients.

There are several potential limitations to this study. One of these is the reliability of esophageal lumen diameter measurement in structured esophagram. In one study using this technique, interobserver variation for measurement of these parameters as assessed by comparing the standard deviation of the difference between the 2 esophagrams in normal subjects was found to be insignificant.[11] Furthermore, all images in this study were interpreted and reviewed by one specialized gastrointestinal radiologist who has been interpreting these esophagrams since the inception of this technique with a standardized protocol using calibration to reduce measurement errors related to magnification. On the other hand, we cannot be assured that

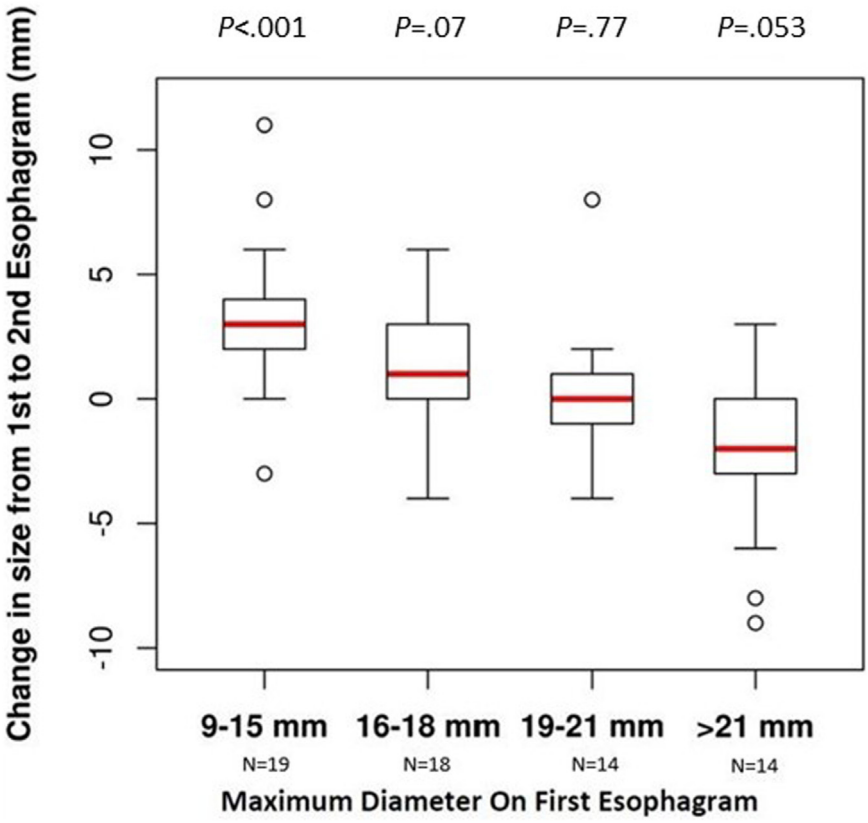

Figure 2. Change in size in maximal esophageal diameter (mm) over study time as a function of initial esophageal diameter.

the accuracy of structured esophagram applies to other medical centers. Another limitation is assuring the continuous use of medical therapy by all patients over years without review of prescription orders or more formal methods of assessing compliance. This study was also retrospective; however, all esophagrams were performed prospectively as a part of the follow-up assessment as previously discussed. Esophageal symptoms were not assessed at the time of esophagram as another meaningful endpoint. On the other hand, there is a poor correlation of symptoms to degree of mucosal eosinophilia, and the compensatory eating maneuvers of EoE patients often mask the severity of strictures. Finally, with a small sample size of patients to study there is concern for inadequate power for our calculations. Although our database of patients with EoE is robust, we chose a group of patients starting in 2002 to ensure a long follow-up period. This was a time when the diagnosis of EoE was early in its recognition, in addition to our use of a structured esophagram.

Conclusion

Long-term improvement in esophageal strictures in patients with EoE may occur, but it is modest and likely occurs over a period of years. Conversely, progression also appears to be minimal. Continuous medical treatment appears to reduce the rate of stricture recurrence and may improve stricture diameter over time. Although these results may reflect a reduction in inflammation, they likely also represent the static or slowly resolving process of fibrosis.

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Correspondence:
Address correspondence to: David A. Katzka, MD, Division of Digestive and Liver Disease, Columbia University, 622 West 168th Street, New York, New York 10032. e-mail: dak2178@cumc.columbia.edu.

Authors' Contributions:
Diana L. Snyder contributed to the study design and coordination, acquisition and interpretation of data, analysis, and drafting of the manuscript. Jeffrey A. Alexander contributed to the design of the esophagram protocol, design and coordination of the study, interpretation and analysis of data, and revision of manuscript for intellectual content. Karthik Ravi contributed to the design and coordination of the study, acquisition, analysis, interpretation of data, and revision of manuscript for intellectual content. Jeff L. Fidler contributed to the design of the esophagram protocol, data acquisition, and critical revision of the manuscript for important intellectual content. David A. Katzka contributed to the design of the esophagram protocol, design and coordination of the study, interpretation and analysis of data, and revision of manuscript for intellectual content. All authors had full access to the data and reviewed the manuscript.

Conflicts of Interest:
These authors disclose the following: Jeffrey A. Alexander has financial interest in Meritage Pharmacia and consults for Lucid Technologies. David A. Katzka receives honoraria from Medtronics and Sanofi and is a member of the Board of Editors. Their paper was handled in accordance with our conflict of interest policy. See https://www.ghadvances.org/content/authorinfo#conflict_of_interest_policy for full details. The remaining authors disclose no conflicts.

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Data, analytic methods, and study material may be made available to other researchers.

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