

Original Article

## Diffuse Esophageal Narrowing in Eosinophilic Esophagitis: A Barium Contrast Study

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### Abstract

**Background:** Patients with eosinophilic esophagitis (EoE) present with mechanical type dysphagia. Barium esophagrams occasionally demonstrate focal strictures or multiple concentric rings. Diffuse narrowing has also been reported but may be difficult to recognize because of lack of normative data.

**Aim:** The aim of this study is to assess esophageal diameters at multiple sites in healthy controls in comparison with EoE patients.

**Methods:** A standardized barium swallow was performed in 22 healthy male volunteers without esophageal symptoms and compared with 10 untreated EoE patients. A radiopaque ruler attached at the subject's back was used to measure maximal esophageal diameter at three esophageal sites by a blinded observer. Peak intraepithelial eosinophil counts and Mayo Dysphagia Questionnaire scores were correlated to esophageal diameters in EoE patients.

**Results:** Two of 10 EoE patients had areas of focal narrowing on barium Xray. Esophageal diameters were significantly less at all three esophageal sites in EoE patients compared with controls. Using a total esophageal diameter score (i.e., sum of the three diameters) to establish the 95th percentile for minimal diameter in controls, four of 10 EoE patients fell below the normal range. There was no significant correlation between esophageal diameters, peak eosinophil counts and any of the Mayo Dysphagia Questionnaire severity scores.

**Conclusion:** Patients with EoE have a diffusely narrow esophagus in comparison to healthy controls, and this abnormality may not be appreciated without using appropriate normative data.

**Keywords:** Barium, Dysphagia, Eosinophils, Esophagus, Stricture, X-ray.

Once considered a rare disorder, eosinophilic esophagitis (EoE) is now recognized as a common cause of solid food dysphagia and food bolus obstruction, particularly in young adult males (1). EoE is diagnosed by the finding of  $\geq 15$  eosinophils per high-powered field on esophageal mucosal biopsies in patients with esophageal symptoms in whom gastroesophageal reflux disease has been excluded (2). Although endoscopy may be normal, a number of macroscopic abnormalities have been described, including linear furrowing, trachealization, focal and diffuse structuring, mucosal trauma and scattered small white exudates (3). Similarly, barium contrast esophagrams may also

be reported as normal in EoE patients, but in some patients, focal strictures (especially proximal strictures) and multiple concentric rings may also be seen (4). The latter is felt to be characteristic of the disorder (5). In addition, a diffusely narrow-calibre esophagus has been described on barium esophagrams in a small subset of EoE patients (6). Focal abnormalities are more readily appreciated by radiologists, and although diffuse narrowing may be recognized when marked, more subtle degrees of diffuse calibre change are likely overlooked, particularly given that we have no well-established normative data on esophageal diameter as measured by barium esophagrams.

Recent studies have provided some useful, albeit limited, objective data in this area (6, 7). Lee et al. (7) reported normal values for esophageal diameter in 10 control subjects and demonstrated that these measures were reproducible. Their standardized protocol involved having subjects rapidly drink a 10-ounce cup of barium, following which they measured the maximal and minimal diameters of the thoracic esophagus at maximal distension. Roughly half of 11 EoE patients studied in an identical fashion were found to have esophageal diameters that fell outside the normal range, and when these patients were subsequently treated with topical steroids, esophageal diameter was seen to normalize. It is noteworthy, however, that the vast majority of patients and controls studied were female, even though EoE is predominantly a disease of young men.

In the current study, we established normal diameters at three different esophageal sites using barium contrast radiography in 22 male control subjects and compared these with 10 male EoE patients.

## METHODS

The study was approved by the research ethics board at Queen's University, and all participants provided informed, written consent. A total of 22 healthy male volunteers were recruited. To be eligible, they had to be free of esophageal symptoms and have no major co-morbid illnesses. Ten male eosinophilic esophagitis patients were recruited. To be eligible, they had to have >15 eosinophils per high-powered field on esophageal mucosal biopsy and be unresponsive to at least a two-month course of proton pump inhibitor therapy. Patients with prior topical steroid treatment or esophageal dilation were excluded. We also excluded patients who had had a recent barium study for clinical indications to avoid repeat X-ray exposure.

### Barium Esophagram Protocol

All participants underwent a standardized barium swallow. They were positioned upright with a radiopaque ruler attached at their back. They were then asked to swallow 150 mL of barium as quickly as possible. Spot films were then obtained when the esophagus appeared maximally distended. The radiologist performing the barium swallow was blinded as to whether the subject was an EoE patient or control, and the spot films were coded and subsequently analyzed by a radiologist who was blinded as to whether the subject was a control or EoE patient. Maximal diameter at three sites (just above the aortic arch, just above the gastroesophageal junction and half way in between) was measured. Eosinophilic esophagitis patients were asked to complete the Mayo dysphagia questionnaire (8).

### Histology

To establish a diagnosis of EoE, biopsies were routinely obtained from both the distal (~2–5 cm above the gastroesophageal junction) and proximal (20–25 cm from the incisors) esophagus.

Hematoxylin phloxine and saffron-stained 5- $\mu$ m-thick sections of endoscopically obtained esophageal mucosal biopsies were reviewed. Eosinophilic inflammation was assessed by counting intraepithelial eosinophils in five separate high-power fields for each case and then calculating the average number of intraepithelial eosinophils for each case. As the eosinophilic inflammation may be variable in intensity and also patchy in distribution, counts were obtained from areas where the intraepithelial inflammation was most intense. Area of actual epithelium within a given microscopic field was not directly controlled (i.e., the actual area of epithelium varied from field to field); however, in all cases, the microscopic field was filled at least 75% by epithelium. This way, the epithelial area between cases that was assessed is considered to be relatively equal, allowing comparison of the eosinophil counts observed.

### Statistical Analysis

Comparisons of baseline demographics and esophageal diameters between controls and EoE subjects was performed using unpaired t-tests. The Spearman rank correlation was used to determine whether there was a correlation between esophageal diameter, mucosal eosinophil counts, parameters of the Mayo dysphagia questionnaire and subject height and esophageal diameter.

## RESULTS

Table 1 summarizes the baseline characteristics of the control and EoE subjects. As can be seen, age, weight and BMI were comparable between the two groups. There was a statistically significant difference in height, with the control group being taller. To determine whether this might have affected our results, we compared the average total esophageal diameter score (i.e., the sum of the diameters in the three esophageal segments) to subject height. No significant correlation was found ( $r=0.1754$ ;  $P=0.43$ , Spearman rank correlation).

Focal radiological abnormalities were noted in only two of the 10 EoE cases, both of whom had focal narrowing in the more proximal esophagus (Figure 1). As can be seen in Figure 2A, EoE patients had a significantly narrowed esophagus at all three levels when compared with controls. In addition, the overall diameter score was significantly less in EoE patients (Figure 2B).

**Table 1.** Baseline characteristics of control subjects and EoE patients.

	Control: mean (range); n=22	EoE: mean (range); n=10	P-value
Age (yrs)	34.3 (18–62)	29.3 (18–51)	0.36
Weight (Kg)	81.9 (54–108)	82 (65–106)	0.88
Height (M)	1.80 (1.7–1.9)	1.74 (1.6–1.9)	0.04
BMI	25.3 (19.7–34.6)	27.4 (21.9–40.2)	0.3
Allergic History	18.2%	45.4%	0.12

To determine what proportion of patients fell outside the normal range, the 95th percentile for the esophageal diameter score was calculated in the control group. In four of the EoE cases, this average diameter fell outside the normal range, including one of the two patients with focal strictures.

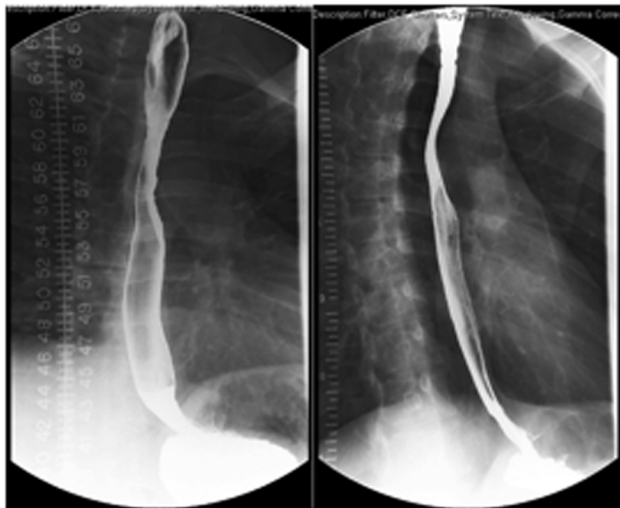


Figure 1. Barium esophograms in the two EoE patients with focal stricturing in the mid to proximal esophagus.

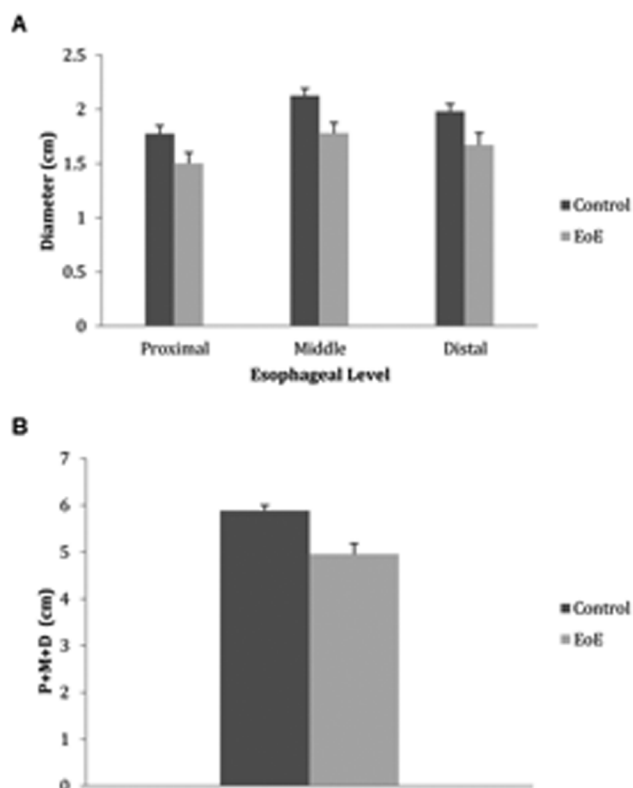


Figure 2. A) The esophageal diameter was significantly less in EoE patients compared with control subjects at all three esophageal locations ( $p=0.046$ ,  $0.006$  and  $0.02$  at the proximal, mid and distal locations, respectively). B) The total diameter score (sum of three diameters) was significantly less in EoE patients ( $p=0.002$ ). Data presented as means  $\pm$  SEM.

It is worth noting that with gross inspection of the barium esophagram, it is relatively easy to miss abnormal studies. Figure 3 is an example of a spot film in an EoE patient and a healthy control. The sum of three diameters in healthy control in this instance was 6.13 cm, whereas in the EoE patient, it was 3.64 cm.

Table 2 summarizes correlations between esophageal diameter, eosinophil counts and Mayo dysphagia questionnaire symptom scores in the patients with EoE. There is no statistical correlation between diameter and any of these parameters. Overall, symptoms scores were not particularly high, with an average composite score (severity  $\times$  frequency) of 9.4 (range 3.33–26), with a maximum possible score of 56.

## DISCUSSION

The present study demonstrates EoE subjects tend to have a diffusely narrowed esophagus when compared with appropriately matched control subjects and suggests that this abnormality may be underreported both clinically and in the literature. Esophageal diameters were significantly less in each of the proximal mid and distal esophageal segments in EoE patients versus controls, and four of 10 subjects fell outside the normal range for average esophageal diameter as established by the 95th percentile values in controls.

Focal (especially proximal) esophageal strictures and multiple concentric rings are seen infrequently on barium studies in EoE patients but are readily apparent when present (Figure 1). A so-called narrow caliber esophagus has also been described in EoE patients, but because there is very limited data as to what constitutes a normal esophageal diameter on barium contrast studies, it is likely that this abnormality is reported only when the

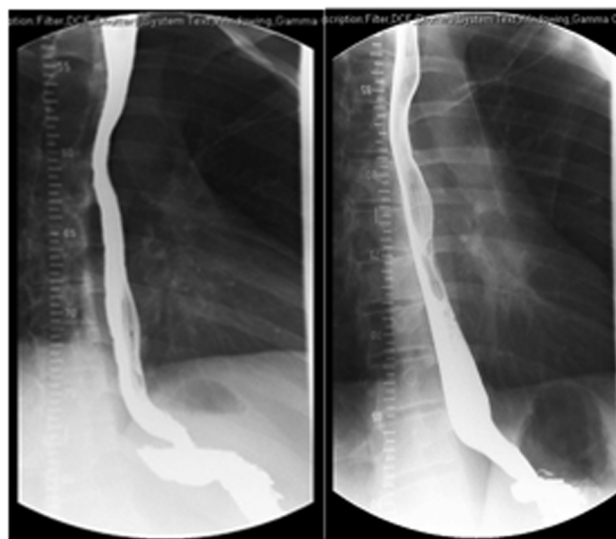


Figure 3. Example of barium esophograms in a healthy control subject (right) and a patient with EoE (left). Although the images look comparable, the sum of the diameters from the three esophageal locations was 6.13 cm in the control subject and 3.64 cm in the EoE patient.

**Table 2.** Correlations (Pearson) between esophageal diameter, eosinophil counts and Mayo dysphagia questionnaire symptom scores in EoE patients.

Variable	Average esophageal diameter	P-value	Smallest esophageal diameter	P-value
Maximum eosinophil count	-0.438	0.238	-0.589	0.095
Dysphagia severity	0.120	0.776	0.284	0.496
Dysphagia frequency	0.119	0.779	0.291	0.485
Frequency x Severity	0.148	0.726	0.258	0.537
Dysphagia duration	0.337	0.415	-0.139	0.742
# foods avoided	0.378	0.356	0.527	0.179
Meal duration	0.018	0.966	-0.228	0.587

diffuse narrowing is severe and that milder degrees of narrowing are overlooked. This is supported by the current study in which 40% of our EoE patients had an abnormally narrow esophagus.

Other groups have reported normal values for barium esophagram using standardized techniques, but the available data to date is quite limited. White et al. (6) used their radiological database to select 10 normal barium X-ray studies to develop normal values that they then compared with a small group of EoE patients. Unfortunately, this normal group was not characterized in terms of possible esophageal symptoms and may not represent a true control group in a healthy asymptomatic population. Subsequently, Lee et al. (7) performed standard barium X-rays in 10 subjects in order to establish normal values for maximum and minimum diameters as measured when the esophagus was maximally distended after the subject rapidly ingested 10 ounces of barium. Using the 10th and 90th percentile in their control group, they established the normal range for minimal esophageal diameter as 15.6–23.7 mm, and the normal range of maximal esophageal diameter as 21–27 mm. These investigators also repeated the measurement and established the technique was reproducible. Approximately half of the 11 EOE patients that they studied in an identical fashion were found to have esophageal diameters that fell below this normal range. Interestingly, when following treatment with topical steroids, esophageal diameter tended to normalize in the subgroup of patients that had initially narrowed esophagus. Of note, this study was atypical in that only two of their 10 control subjects and three of their 11 EoE patients were males, which is not representative of the EoE population that generally is reported as being 70% or more male. Our study is unique in that we prospectively recruited control subjects and deliberately selected males given the demographics of the disease. We also measured maximal diameter at three different sites along the esophagus because we were interested in picking up diffuse rather than focal narrowing. Furthermore, we deployed a radiopaque ruler superimposed over the esophagus in order to improve the accuracy of our diameter measurements.

EoE patients typically present with a mechanical type dysphagia and food bolus obstructions even when there is no obvious endoscopic or barium X-ray abnormality. Although motor abnormalities have been described in EoE (9), the nature of the

dysphagia suggests that motor abnormalities likely play a secondary role in the etiology of the dysphagia. Poor compliance has been demonstrated in EoE patients (10) in keeping with the known fibrotic remodeling that can occur in the disease. This lack of distensibility likely results in an inability to accommodate to the passage of larger food boluses and probably plays a fundamental role in the etiology of dysphagia in EoE, reflux and other forms of esophagitis. Diffuse esophageal narrowing, even if subtle, may well be the radiological equivalent of poor compliance. We suspect that in the six patients with esophageal diameters that fell within the normal range, impaired compliance likely played a key role in the pathogenesis of their dysphagia.

In the current study, we found no significant correlations between the average esophageal diameter in EoE patients and eosinophil cell count or any of the metrics on the Mayo dysphagia questionnaire. This is perhaps not surprising given the relatively small number of patients studied and the nature of the Mayo Dysphagia Questionnaire. Although comprehensive and useful for measuring the impact of dysphagia on a patient, this questionnaire is subjective and likely lacks precision with respect to assessing objective severity of disease. Furthermore, the perception of dysphagia is undoubtedly influenced by sensory and supratentorial factors.

In summary, although endoscopy with esophageal biopsies is required to confirm a diagnosis of EoE, timely access to endoscopy is a problem in some regions, resulting in many patients still being referred for barium contrast studies. The current study demonstrates that diffuse esophageal narrowing can be detected in a significant subset of EoE patients using a simple technique that can be readily implemented by radiology departments. Establishing normal values for esophageal diameter using contrast radiology has the potential to improve the diagnostic efficacy of barium X-rays in this and other esophageal disorders.

### Acknowledgements

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## Conflicts of Interest

Authors have no conflicts of interest to declare.

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