Dilation modifies association between symptoms and esophageal eosinophilia in adult patients with eosinophilic esophagitis

Ekaterina Safroneeva, PhD[1], Cary C. Cotton, MD MPH[2], Alain M. Schoepfer, MD[3], Marcel Zwahlen, PhD[1], John T. Woosley, MD[4], Evan S. Dellon, MD, MPH[2]

[1]Institute of Social and Preventive Medicine, University of Bern, Switzerland [2]Center for Esophageal Diseases and Swallowing, Division of Gastroenterology and Hepatology, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC, United States [3]Division of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne, Lausanne, Switzerland [4]Department of Pathology and Laboratory Medicine, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC, United States

Abstract

Background and aims—We investigated whether dilation modifies the association between symptoms and esophageal eosinophilia (eos/hpf) in eosinophilic esophagitis (EoE) patients enrolled into randomized trial comparing efficacy of budesonide and fluticasone.

Methods—Baseline DSQ and EEsAI were available in 102 and 73 patients, respectively, of whom 56 and 39 underwent dilation at screening endoscopy before symptom assessment. The pair-wise relationship between DSQ, EEsAI, and eos/hpf was analyzed with nonparametric correlations.

Results—In non-dilated patients, the association between baseline eos/hpf and symptoms was moderate and significant, whilst it was abolished in dilated patients.

Conclusion—Dilation modifies association between symptoms and eos/hpf. (clinicaltrials.gov NCT02019758)

Keywords

eosinophilic esophagitis; dysphagia; dysphagia symptom questionnaire; eosinophilic esophagitis activity index; esophageal eosinophilia; correlation

INTRODUCTION

Esophageal dilation is used to manage adults with eosinophilic esophagitis (EoE).[1,2,3,4] Using a non-validated dysphagia measure in patients managed with dilation alone, Schoepfer *et al.* observed a median post-dilation dysphagia improvement lasting 12 months.[5] To date, dilation effect on symptoms has not been evaluated by patient-reported outcomes (PROs), including Dysphagia Symptom Questionnaire (DSQ) and Eosinophilic Esophagitis Activity Index (EEsAI).

We investigated whether dilation modifies the association between symptoms assessed using validated PROs and esophageal eosinophilia in EoE adults enrolled into a randomized trial comparing budesonide and fluticasone (NCT02019758).[6]

METHODS

Dilation was allowed during the screening endoscopy before symptom assessment at baseline. The pair-wise relationship between DSQ (0 to 84; 24-hour recall), EEsAI (0 to 100; 7-day recall), EoE Endoscopic Reference Score (EREFS), and peak esophageal eosinophils/high-power field (eos/hpf) was analyzed with nonparametric correlations.[7,8,9,10,11] We used linear regression with eos/hpf as the outcome, EEsAI and DSQ as predictors, and an interaction for dilation and symptoms (see Supplementary Materials).

RESULTS

Of the 111 trial patients, 102 patients completed DSQ 4 days over 7-day period at baseline and 73 patients completed EEsAI (Suppl.Figure 1). At baseline, DSQ, EREFS, and eos/hpf were similar between the two groups (Suppl.Table 1).

When assessing the relationship between DSQ, DSQ subscales, maximum dysphagia days/week, and eos/hpf at baseline (n=102) (Figure 1, Suppl.Table 2), we observed weak associations between eos/hpf and dysphagia symptoms. We observed moderate associations between the eos/hpf and dysphagia symptoms in non-dilated patients and no association between these in dilated patients. When examining the association between changes from baseline to end of treatment (EOT) in eos/hpf and DSQ (n=79), trends were similar.

When analyzing subjects completing DSQ and EEsAI at baseline (n=73) (Figure 2, Suppl.Table 2, Suppl.Figure 2), we observed moderate to strong associations between DSQ and EEsAI scores regardless of dilation status. Irrespective of PRO used, we observed moderate correlations between symptoms and eos/hpf in non-dilated patients and no association in dilated patients.

For a 10-unit DSQ increase in non-dilated patients, the predicted log-transformed eos/hpf increased by 27.1% (p-value=0.016) (Suppl.Table 3). For a 10-unit DSQ increase in dilated patients, the predicted eos/hpf decreased by 7.7% (p-value=0.398). When assessing the association between change in symptoms and eos/hpf from baseline to EOT (Suppl.Table 4; positive coefficient indicates PRO improvement or inflammation reduction), we found that predicted eos/hpf improves by 21 cells per 10-point DSQ improvement in non-dilated

patients (p-value=0.016). In dilated patients, predicted eos/hpf decreased by 4 cells per 10-point DSQ improvement (p-value=0.511). The trends for DSQ subcomponents were similar.

The relationship between baseline dysphagia and predicted eos/hpf, and between change from baseline to EOT in dysphagia and predicted eos/hpf, is illustrated in Figure 3. Single variable linear regression analyses for non-dilated patients (46/102) at baseline and (32/79) at EOT are in Suppl.Table 5.

We observed no associations between PROs and EREFS at baseline and for changes in EREFS and PRO from baseline to EOT regardless of dilation status.

DISCUSSION

Dilation performed before symptom assessment modifies the associations between baseline eos/hpf and symptom severity and between the change from baseline to EOT in these parameters. In non-dilated patients, the association between esophageal eosinophilia and symptom severity is moderate, and it is abolished in dilated patients.

The dilation effects likely last ~12 months.[5] These findings are corroborated in a multicenter observational adult cohort, in which no association between symptom and eos/hpf in dilated patients and a moderate association in non-dilated patients was found.[12]

These are *post-hoc* analyses; hence, our findings should be regarded as observational. The interaction term between EEsAI-assessed symptoms and dilation was not significant in the 73-patient subset. The study limitations are countered by sound methodology and the fact that data come from a small, rigorously conducted RCT, during which validated endpoints were used.

Dilation modifies the association between eos/hpf and symptom severity. Consideration should be given to stratified randomization on dilation status at baseline in studies assessing efficacy of anti-inflammatory therapies in EoE patients, and monitoring symptoms only as a treatment outcome should be discouraged after dilation in the clinical setting.[13,14]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations

Adj.	adjusted
CI	confidence interval
DSQ	dysphagia symptom score
EEsAI	eosinophilic esophagitis activity index
eos/hpf	peak esophageal eosinophil counts per high-power filed
EREFS	endoscopic reference score
IQR	interquartile range
PRO	patient-reported outcomes

REFERENCES

1. Lucendo AJ, Molina-Infante J, Arias Á, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. United European Gastroenterol J. 2017;5:335–358.

2. Dellon ES, Gonsalves N, Hirano I, et al. ACG clinical guideline: Evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). Am J Gastroenterol. 2013;108:679–92. [PubMed: 23567357]

3. Runge TM, Eluri S, Cotton CC, et al. Outcomes of Esophageal Dilation in Eosinophilic Esophagitis: Safety, Efficacy, and Persistence of the Fibrostenotic Phenotype. Am J Gastroenterol 2016;111:206–13. [PubMed: 26753894]

4. Dougherty M, Runge TM, Eluri S, Dellon ES. Esophageal dilation with either bougie or balloon technique as a treatment for eosinophilic esophagitis: a systematic review and meta-analysis. Gastrointest Endosc 2017;86:581–91. [PubMed: 28461094]

5. Schoepfer AM, Gonsalves N, Bussmann C, et al. Esophageal dilation in eosinophilic esophagitis: effectiveness, safety, and impact on the underlying inflammation. Am J Gastroenterol. 2010;105:1062–70. [PubMed: 19935783]

6. Dellon ES, Woosley JT, Arrington A, et al. Efficacy of Budesonide vs Fluticasone for Initial Treatment of Eosinophilic Esophagitis in a Randomized Controlled Trial. Gastroenterology. 2019;157:65–73. [PubMed: 30872104]

7. Schoepfer AM, Straumann A, Panczak R, et al. Development and validation of a symptom-based activity index for adults with eosinophilic esophagitis. Gastroenterology. 2014;147:1255–66. [PubMed: 25160980]

8. Dellon ES, Irani AM, Hill MR, Hirano I. Development and field testing of a novel patient-reported outcome measure of dysphagia in patients with eosinophilic esophagitis. Aliment Pharmacol Ther. 2013;38:634–42. [PubMed: 23837796]

9. 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. [PubMed: 22619364]

10. Dellon ES, Cotton CC, Gebhart JH, et al. Accuracy of the Eosinophilic Esophagitis Endoscopic Reference Score in Diagnosis and Determining Response to Treatment. Clin Gastroenterol Hepatol 2016;14:31–9. [PubMed: 26404868]

11. Dellon ES, Fritchie KJ, Rubinas TC, et al. Inter- and intraobserver reliability and validation of a new method for determination of eosinophil counts in patients with esophageal eosinophilia. Dig Dis Sci 2010;55:1940–9. [PubMed: 19830560]

12. Safroneeva E, Aceves SS, King E, et al. Mo1187 Dilation reduces positive correlation between symptoms and histologic findings in adults with eosinophilic esophagitis. Gastroenterology 2020;158:S–819.

13. Dellon ES, Gupta SK. A conceptual approach to understanding treatment response in eosinophilic esophagitis. Clin Gastroenterol Hepatol 2019;17:2149–60. [PubMed: 30710696]

14. Runge TM, Eluri S, Woosley JT, et al. Control of inflammation decreases the need for subsequent esophageal dilation in patients with eosinophilic esophagitis. Dis Esophagus. 2017;30:1–7.
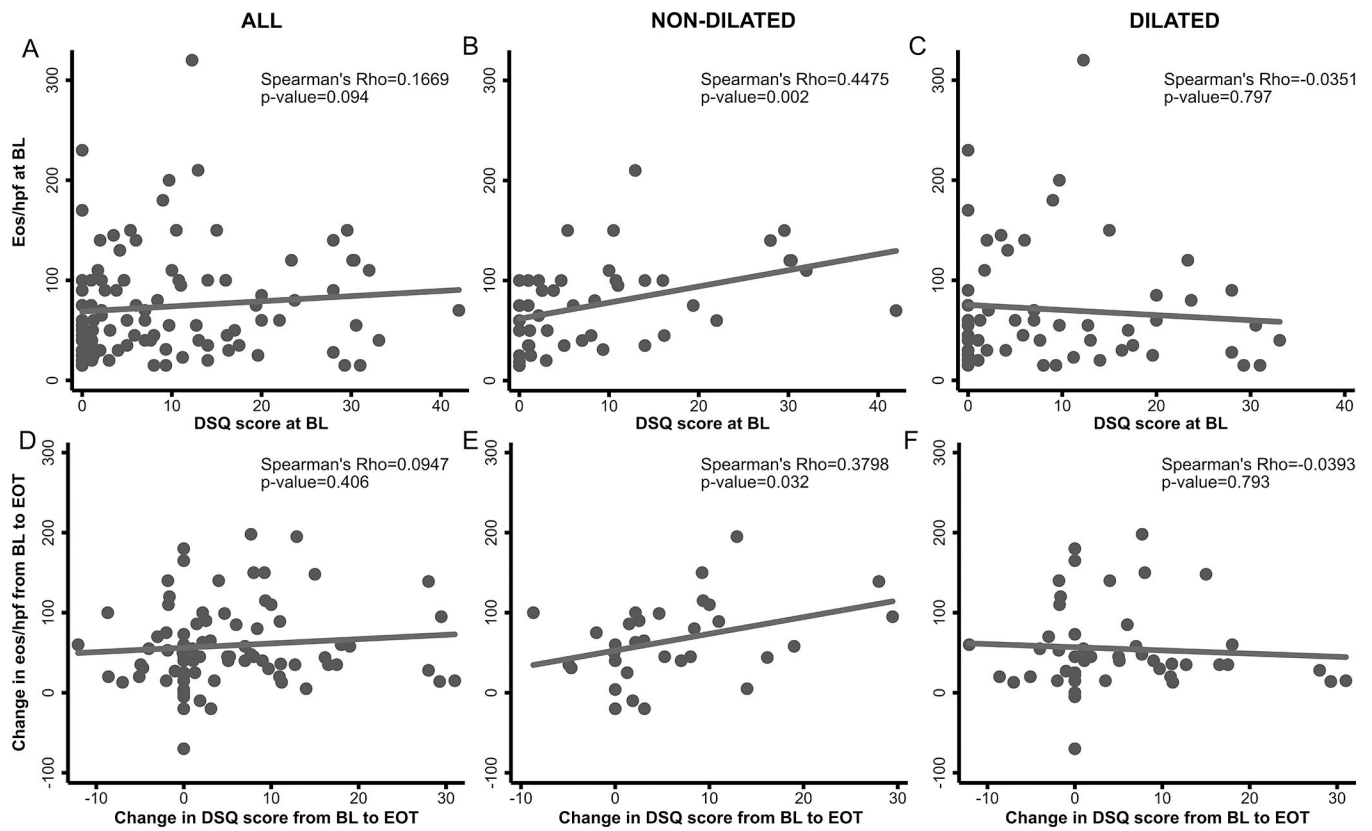
Figure 1.
Relationship between baseline DSQ and esophageal eosinophilia in all patients (n=102) (**A**), in patients that did not undergo dilation (n=46) (**B**), and in patients that were dilated (n=56) (**C**) at study baseline. Relationship between change from baseline to end of treatment in DSQ and esophageal eosinophilia in all patients (n=79) (**D**), in patients that did not undergo dilation (n=32) (**E**), and in patients that were dilated (n=47) (**F**) at screening endoscopy.
Abbreviations: BL, baseline; DSQ, dysphagia symptom score; EOT (end of treatment).
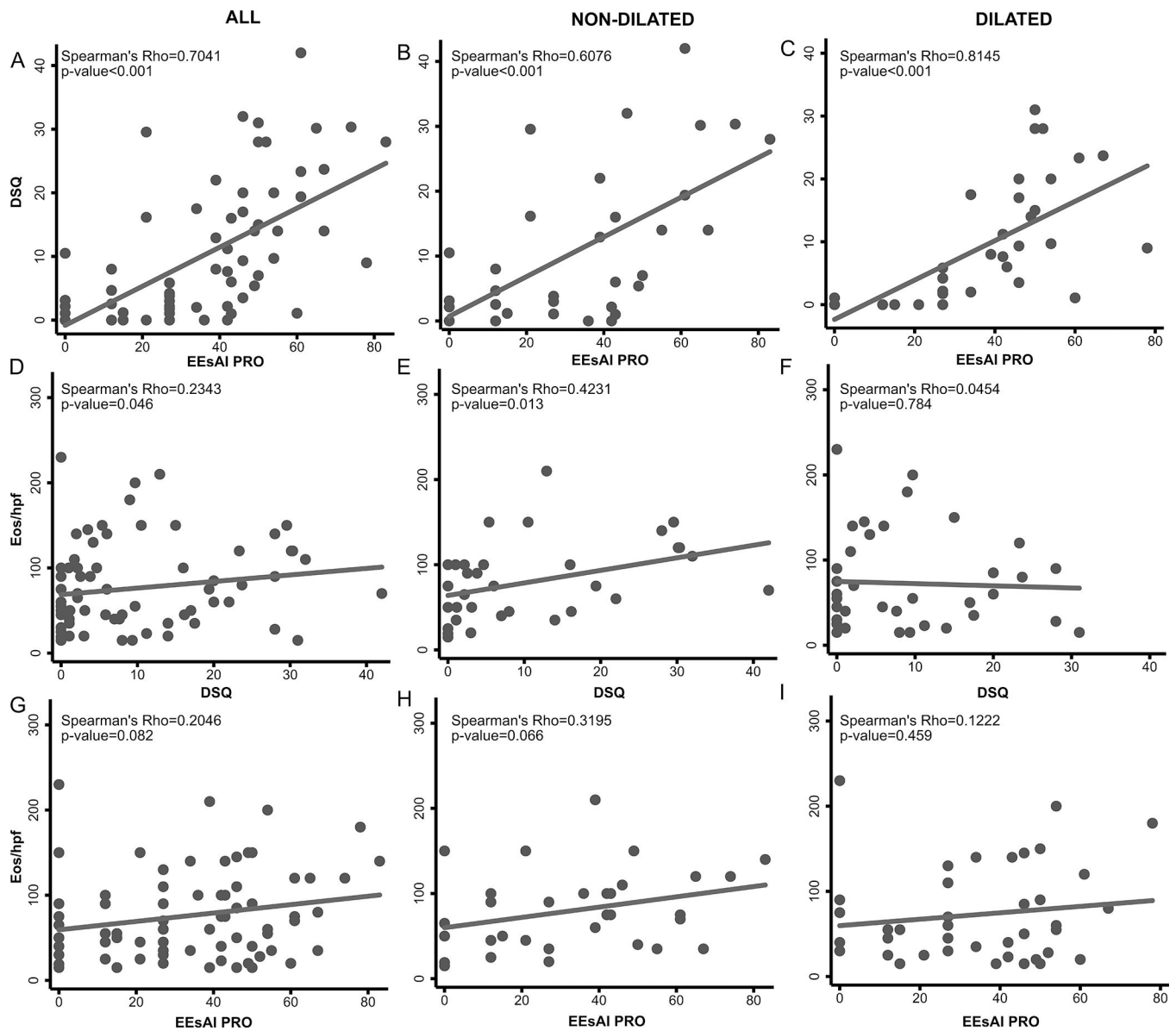
Figure 2.
Relationship between baseline DSQ and EEsAI PRO in all patients (n=73) (**A**), in patients
that did not undergo dilation (n=34) (**B**), and in patients that were dilated (n=39) (**C**) at study
baseline. Relationship between baseline DSQ and esophageal eosinophilia in all patients
(**D**), in patients that did not undergo dilation (**E**), and in patients that were dilated (**F**) at
screening endoscopy. Relationship between baseline EEsAI PRO and esophageal
eosinophilia in all patients (**G**), in patients that did not undergo dilation (**H**), and in patients
that were dilated (**I**) at study baseline. **Abbreviations:** DSQ, dysphagia symptom score;
EEsAI PRO, eosinophilic esophagitis activity index patient-reported outcomes instrument.
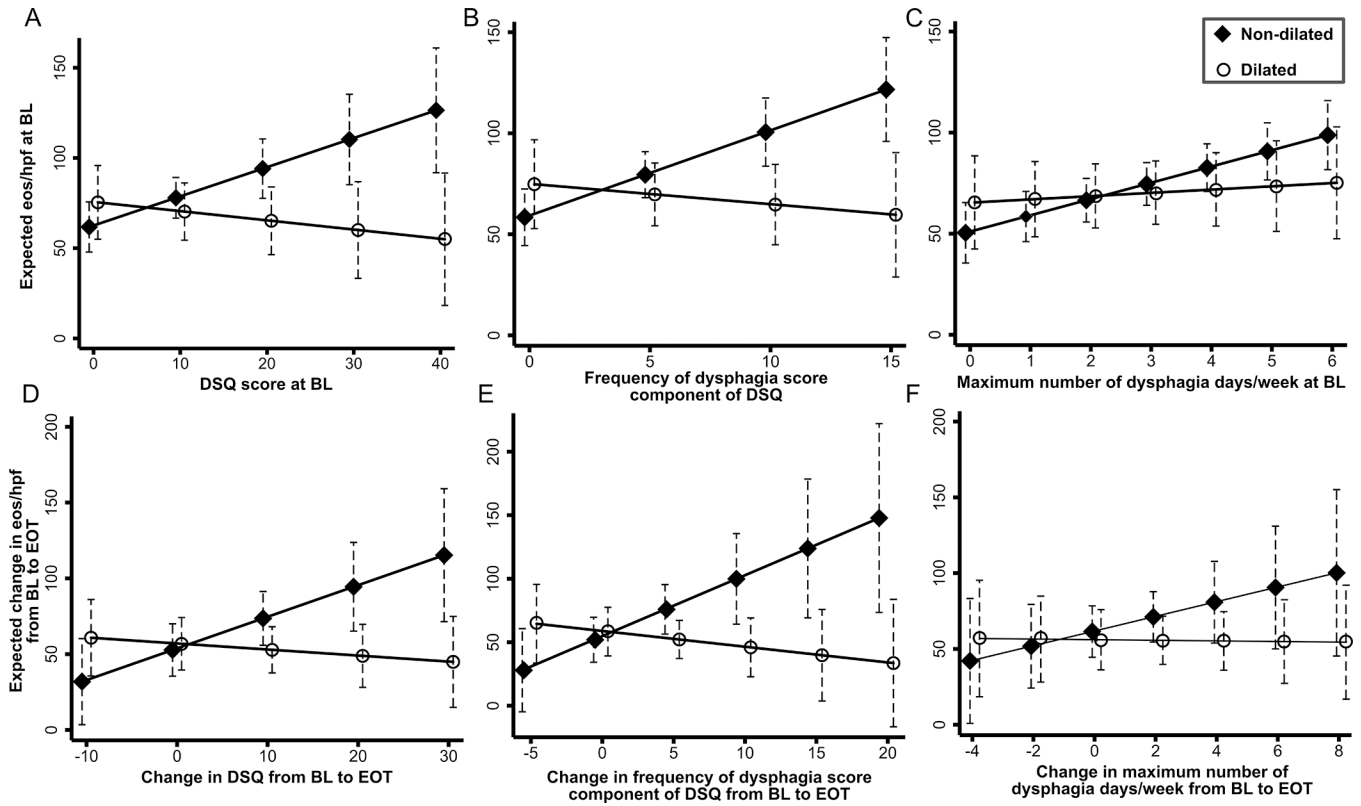
Figure 3.
The margin plot of expected esophageal eosinophilia stratified on dilation (n=102) by DSQ
(**A**), dysphagia frequency component of DSQ (**B**), and maximum number of dysphagia days
per week (**C**) at study baseline. The predictive margins of change from baseline to end of
treatment in esophageal eosinophilia stratified on dilation (n=79) by change in DSQ (**D**), by
change in dysphagia frequency component of DSQ (**E**), and by change in maximum number
of dysphagia days per week (**F**). **Abbreviations:** BL, baseline; DSQ, dysphagia symptom
score EOT (end of treatment).

[a] (**A**) in non-dilated patients with the DSQ score of 10 and 30 points, predicted values of 77
eos/hpf and 110 eos/hpf, respectively, are observed (**A**). In dilated patients with the DSQ
score of 10 and 30 points, predicted values of 70 eos/hpf and 60 eos/hpf, respectively, are
observed.

[b] (**B**) in non-dilated patients with maximum dysphagia days of 2, 4, and 6, predicted values
of 67, 83, and 99 eos/hpf, respectively, are observed. In dilated patients with maximum
dysphagia days of 2, 4, and 6, predicted values of 69, 72, and 75 eos/hpf, respectively, are
observed.