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

Short title: modifying effect of dilation on association between symptoms and esophageal eosinophilia

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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.

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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)

Word count: 100

Key words: 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.

131 The dilation effects likely last ~12 months.[5] These findings are corroborated in a
132 multicenter observational adult cohort, in which no association between symptom and
133 eos/hpf in dilated patients and a moderate association in non-dilated patients was found.[12]
134 These are *post-hoc* analyses; hence, our findings should be regarded as observational.
135 The interaction term between EEsAI-assessed symptoms and dilation was not significant in
136 the 73-patient subset. The study limitations are countered by sound methodology and the
137 fact that data come from a small, rigorously conducted RCT, during which validated
138 endpoints were used.
139 Dilation modifies the association between eos/hpf and symptom severity. Consideration
140 should be given to stratified randomization on dilation status at baseline in studies assessing
141 efficacy of anti-inflammatory therapies in EoE patients, and monitoring symptoms only as a
142 treatment outcome should be discouraged after dilation in the clinical setting.[13,14]
143

SUPPLEMENTARY TABLES

Supplementary Table 1: Patient characteristics at baseline.

Characteristics	Median, IQR, range or Frequency (%) n=102 (DSQ group)	Median, IQR, range or Frequency (%) n=73 (DSQ + EEsAI group)
Age	39 (IQR [26, 51], range 16– 73)	41 (IQR [28, 52], range 17– 73)
Male	68 (67)	53 (73)
White	98 (96)	71 (97)
Any atopic conditions	77 (75)	55 (75)
Length of dysphagia prior to diagnosis (years)	8 (IQR [4, 14], range 0-49)	8 (IQR [4, 15], range 0-38)
Maximum dysphagia days	3 (IQR [1.0, 5.6], range 0 – 7)	3 (IQR [0, 5.6], range 0 – 7)
DSQ score	6.00 (IQR [1.08, 14], range 0 - 42)	5.83 (IQR [1, 16], range 0 - 42)
EEsAI PRO	39 (IQR [15, 50], range 0 - 83) (n=73)	39 (IQR [15, 50], range 0 - 83)
Eos/hpf	60 (IQR [35, 100], range 15 – 320)	60 (IQR [35, 100], range 15 – 230)
EREFS	5 (IQR [3, 6], range 0 – 8)	5 (IQR [3, 6], range 0 – 8)
Dilation required at baseline	56 (55%)	39(53%)

Abbreviations: DSQ, dysphagia symptom questionnaire; EEsAI, eosinophilic esophagitis activity index; esophageal eosinophilia per high-power field (eos/hpf); EREFS, endoscopic reference score; IQR, interquartile range.

Supplementary Table 2. The Spearman's correlations (Rho) between dysphagia assessed using DSQ and esophageal eosinophilia at baseline, between changes from baseline to end of treatment in dysphagia assessed in DSQ and esophageal eosinophilia, dysphagia assessed using EEsAI PRO and DSQ, as well as between dysphagia measures and esophageal eosinophilia at baseline. We applied the following definitions to interpret the Spearman's correlation coefficient: ≤0.3, weak; >0.3-<0.7 moderate; ≥0.7, strong relationship.

DSQ only	**All**		**Non-dilated**		**Dilated**	
Baseline	**Rho**	**p-value**	**Rho**	**p-value**	**Rho**	**p-value**
Eos/hpf vs. PRO	**n=102**		**n=46**		**n=56**	
Eos/hpf vs. dysphagia days	0.216	0.030	0.477	0.001	0.029	0.831
Eos/hpf vs. DSQ score	0.167	0.094	0.448	0.002	-0.035	0.797
Eos/hpf vs. Dysphagia frequency	0.185	0.062	0.432	0.003	0.005	0.969
Eos/hpf vs. Strategy of dealing with dysphagia	0.160	0.109	0.433	0.003	-0.021	0.876
Change from baseline to end of treatment	**Rho**	**p-value**	**Rho**	**p-value**	**Rho**	**p-value**
∆Eos/hpf vs. ∆PRO	**n=79**		**n=32**		**n=47**	
∆Eos/hpf vs. ∆dysphagia days (n=72/28/44)	0.060	0.617	0.231	0.237	0.001	0.997
∆Eos/hpf vs. ∆DSQ score	0.095	0.406	0.380	0.032	-0.039	0.793
∆Eos/hpf vs. ∆Dysphagia frequency	0.071	0.533	0.362	0.042	-0.078	0.602
∆Eos/hpf vs. ∆Strategy of dealing with dysphagia	0.081	0.478	0.337	0.059	-0.074	0.623
DSQ and EEsAI Baseline	**Rho**	**p-value**	**Rho**	**p-value**	**Rho**	**p-value**
EEsAI vs. DSQ	**n=73**		**n=34**		**n=39**	
Dysphagia frequency DSQ vs. dysphagia days	0.963	<0.001	0.954	<0.001	0.965	<0.001
EEsAI PRO score vs. DSQ score	0.704	<0.001	0.608	<0.001	0.815	<0.001
Dysphagia frequency EEsAI PRO vs. dysphagia frequency DSQ	0.703	<0.001	0.568	<0.001	0.827	<0.001
EEsAI PRO score vs. dysphagia days	0.667	<0.001	0.5057	0.0023	0.820	<0.001
Dysphagia frequency EEsAI PRO vs. dysphagia days	0.660	<0.001	0.5045	0.0023	0.803	<0.001
DSQ and EEsAI Baseline	**Rho**	**p-value**	**Rho**	**p-value**	**Rho**	**p-value**
Eos/hpf vs. PRO	**n=73**		**n=34**		**n=39**	
Eos/hpf vs. dysphagia days	0.262	0.025	0.486	0.004	0.050	0.763
Eos/hpf vs. DSQ score	0.234	0.046	0.423	0.013	0.045	0.784
Eos/hpf vs. EEsAI PRO score	0.205	0.082	0.320	0.066	0.122	0.459

155 **Abbreviations:** DSQ, dysphagia symptom questionnaire; EEsAI, eosinophilic esophagitis activity index; esophageal
156 eosinophilia per high-power field (eos/hpf).

157

158 **Supplementary Table 3.** Linear regression coefficients, 95% confidence intervals, and p-
159 values for four models of natural log-transformed esophageal eosinophilia as outcome in 102
160 patients, in whom the baseline data on all subcomponents of DSQ were available.

	Coefficient [95% CI]	p-value	R^{2d}	Constant[c] [95% CI]	% change in eos/hpf for every unit ↑ in symptoms
Model 1: Dysphagia days × Dilation as predictors					
[a]**Dysphagia days (normalized to over 7 days)**	0.119 [0.037, 0.202]	0.005	0.073 [a]	3.780 [3.437, 4.123]	In non-dilated, ↑12.6%
Dilation within 3 months of baseline	0.144 [-0.302, 0.591]	0.522			
Dilation within 3 months of baseline x Dysphagia days	-0.111 [-0.218, 0.003]	0.044			
([b]**Adjusted coefficient for dysphagia days in dilated patients)**	0.009 [0.060, 0.077]	0.796			In dilated, ↑0.9%
Model 2: DSQ score × Dilation as predictors					
[a]**DSQ (per 10-point)**	0.240 [0.045, 0.435]	0.016	0.060 [a]	3.948 [3.671, 4.225]	In non-dilated ↑27.1%
Dilation within 3 months of baseline	0.080 [-0.296, 0.455]	0.674			
Dilation within 3 months of baseline x DSQ	-0.320 [-0.590, 0.050]	0.021			
([b]**Adjusted coefficient for DSQ in dilated patients)**	-0.080 [-0.267, 0.107]	0.398			In dilated, ↓7.7%
Model 3: Dysphagia frequency based on DSQ × Dilation as predictors					
[a]**Dysphagia frequency (DSQ)**	0.065 [0.014, 0.117]	0.014	0.059 [a]	3.887 [3.578, 4.195]	In non-dilated ↑6.7%
Dilation within 3 months of baseline	0.120 [-0.283, 0.524]	0.555			
Dilation within 3 months of baseline x Dysphagia frequency (DSQ)	-0.078 [-0.146, -0.010]	0.025			
([b]**Adjusted coefficient for dysphagia frequency in dilated patients)**	-0.013 [-0.058, 0.031]	0.562			In dilated, ↓1.3%
Model 4: Strategy of dealing with dysphagia (DSQ) × Dilation as predictors					
[a]**Strategy of dealing with dysphagia (DSQ)**	0.043 [0.004, 0.082]	0.032	0.048 [a]	4.019 [3.766, 4.271]	In non-dilated ↑4.4%
Dilation within 3 months of baseline	-0.002 [-0.347, 0.342]	0.990			

Dilation within 3 months of baseline x Strategy of dealing with dysphagia (DSQ)	-0.060 [-0.115, -0.005]	0.033			
([b]Adjusted coefficient for Strategy of dealing with dysphagia (DSQ) in dilated patients)	-0.017 [-0.055, 0.022]	0.386			In dilated, ↓1.7%

[a] The coefficient represents the change in the value of the predicted change in natural log-transformed eos/hpf for each category change of the independent variable. For example, for a 10-point increase in the baseline value of DSQ score, the predicted esophageal eosinophilia improved (dropped) by 27.1% in non-dilated patients (e to the power of the coefficient, $e^{0.24}$=1.271, means increase of 27.1%).

[b] Adjusted coefficient for estimating increase in symptom score in dilated patients. For example, for a 10-point improvement in the baseline value of DSQ score, the predicted esophageal eosinophilia deteriorated (increased) by 7.7% in dilated patients (e to the power of the coefficient, $e^{-0.08}$=0.923, 1-0.923, means decrease of 7.7%).

[c] The constant represents the value of the predicted change from baseline to end of treatment in esophageal eosinophilia when all values of independent variables are set to zero or reference category.

[d] The coefficient of determination, R^2 is a measure of the extent to which the regression model describes the observed data. The closer the R^2 is to 1, the more precise the regression model is. Because R^2 can be made artificially high by including a large number of independent variables that have an apparent effect purely by chance, adjusted R^2 for the number of terms included into the model is provided.

[e] The underlying assumption for including continuous variables, such as esophageal eosinophilia, in the linear regression is that the residuals are linear. By log-transforming peak esophageal eosinophilia at baseline, the residuals were more linear and the fit of the model was improved. This kind of transformation is often performed for cell counts in blood.

Abbreviations: Adj., adjusted; CI, confidence interval; DSQ, dysphagia symptom score; EEsAI, eosinophilic esophagitis activity index.

Supplementary Table 4. Linear regression coefficients, 95% confidence intervals, and p-values for the models of change in esophageal eosinophilia from baseline to end of treatment as outcome in 79 patients, in whom the baseline and end of treatment data on all subcomponents of DSQ were available.

	Coeff. [95% CI]	p-value	R^{2d}	Constant[c] [95% CI]
Model 1: ΔDysphagia days × Dilation as predictors				
[a]**ΔDysphagia days (normalized to over 7 days) (n=72)**	4.842 [-3.063, 12.749]	0.226	0.041	61.467 [43.828, 79.107]
Dilation within 3 months of baseline	-5.397 [-32.571, 21.777]	0.693		
Dilation within 3 months of baseline x ΔDysphagia days	-5.043 [-14.962, 4.876]	0.314		
([b]Adjusted coefficient for Δdysphagia days in dilated patients)	-0.201 [-6.191, 5.789]	0.947		
Model 2: ΔDSQ score × Dilation as predictors				
[a]**ΔDSQ (per 10 points)**	20.856 [4.069, 37.644]	0.016	0.060	52.733 [34.833, 70.633]
Dilation within 3 months of baseline	4.111 [-21.242, 29.467]	0.748		
Dilation within 3 months of baseline x ΔDSQ	-24.835 [-45.470, -4.200]	0.019		
([b]Adjusted coefficient for ΔDSQ in dilated patients)	-3.979 [-15.978, 8.020]	0.511		
Model 3: ΔDysphagia frequency based on DSQ × Dilation as predictors				
[a]**ΔDysphagia frequency (DSQ)**	4.794 [0.585, 9.004]	0.026	0.059	51.909 [33.577, 70.261]
Dilation within 3 months of baseline	6.433 [-20.606, 33.472]	0.637		
Dilation x ΔDysphagia frequency (DSQ)	-6.034 [-11.272, -0.795]	0.025		
([b]Adjusted coefficient for Δdysphagia frequency in dilated patients)	-1.239 [-4.358, 1.879]	0.431		
Model 4: ΔStrategy of dealing with dysphagia (DSQ) × Dilation as predictors				
[a]**ΔStrategy of dealing with dysphagia (DSQ)**	3.409 [0.465, 6.353]	0.024	0.051	55.932 [38.004, 73.861]
Dilation within 3 months of baseline	1.120 [-23.878, 26.117]	0.929		
Dilation x ΔStrategy of dealing with dysphagia (DSQ)	-4.314 [-7.975, -0.653]	0.022		
([b]Adjusted coefficient for Δstrategy of dealing with dysphagia (DSQ) in dilated	-0.905 [-3.081, 1.271]	0.410		

patients)				

[a] The coefficient represents the change in the value of the predicted change in eos/hpf for each category change of the independent variable. For example, for a 10-point improvement in the DSQ score from baseline to end of treatment, the predicted esophageal eosinophilia improved (dropped) by 21 cells in non-dilated patients.

[b] Adjusted coefficient for estimating increase in symptom score in dilated patients. For example, for a 10-point improvement in the DSQ score from baseline to end of treatment, the predicted esophageal eosinophilia deteriorated (increased) by 4 cells in dilated patients.

[c] The constant represents the value of the predicted change from baseline to end of treatment in esophageal eosinophilia when all values of independent variables are set to zero or reference category.

[d] The coefficient of determination, R^2 is a measure of the extent to which the regression model describes the observed data. The closer the R^2 is to 1, the more precise the regression model is.

Abbreviations: CI, confidence interval; Coeff., coefficient; ∆, change; DSQ, dysphagia symptom score; EEsAI, eosinophilic esophagitis activity index.

Supplementary Table 5. Single variable linear regression coefficients, 95% confidence intervals, and p-values for the models of esophageal eosinophilia as outcome in non-dilated patients, in whom data on DSQ (n=46) and on DSQ and EEsAI (n=34) was available and for the models of change in esophageal eosinophilia as outcome in 32 non-dilated patients, in whom all the baseline and end of treatment DSQ data were available.

	Coefficient	95% CI	p-value	R^2	Constant [95% CI]	% change in eos/hpf for every unit ↑ in symptoms
N=46						
Dysphagia days (normalized to over 7 days)	0.120	[0.052, 0.187]	0.001	0.224	3.78 [3.50, 4.06]	12.7%
Per 10-points DSQ score	0.240	[0.077, 0.404]	0.005	0.166	3.95 [3.72, 4.18]	27.1%
Dysphagia frequency (DSQ)	0.065	[0.022, 0.108]	0.004	0.175	3.89 [3.63, 4.14]	6.7%
Strategy of dealing with dysphagia (DSQ)	0.043	[0.010, 0.076]	0.013	0.132	4.02 [3.80, 4.23]	4.4%
n=34						
Per 10-points DSQ score	0.224	[-0.042, 0.407]	0.018	0.164	3.93 [3.66, 4.24]	25.1%
Per 10-points EEsAI (7 days)	0.101	[-0.009, 0.193]	0.033	0.134	3.86 [3.49, 4.24]	10.6%
n=32						
ΔDysphagia days (normalized to over 7 days) (n=28)	4.842	[-3.371, 13.056]	0.236	0.079	61.47 [43.14, 79.79]	NA
ΔDSQ (per 10 points)	20.856	[3.537, 38.175]	0.020	0.135	52.73 [34.27, 71.20]	NA
ΔDysphagia frequency (DSQ)	4.794	[0.451, 9.137]	0.032	0.124	51.91 [32.98, 70.84]	NA

ΔStrategy of dealing with dysphagia (DSQ)	3.409	[0.371, 6.446]	0.029	0.105	55.93 [37.44, 74.43]	NA

Abbreviations: CI, confidence interval; DSQ, dysphagia symptom score; EEsAI, eosinophilic esophagitis activity index; NA, not applicable.

206 **FIGURES**

207 **Figure 1.** Relationship between baseline DSQ and esophageal eosinophilia in all patients
208 (n=102) (**A**), in patients that did not undergo dilation (n=46) (**B**), and in patients that were
209 dilated (n=56) (**C**) at study baseline. Relationship between change from baseline to end of
210 treatment in DSQ and esophageal eosinophilia in all patients (n=79) (**D**), in patients that did
211 not undergo dilation (n=32) (**E**), and in patients that were dilated (n=47) (**F**) at screening
212 endoscopy. **Abbreviations:** BL, baseline; DSQ, dysphagia symptom score; EOT (end of
213 treatment).

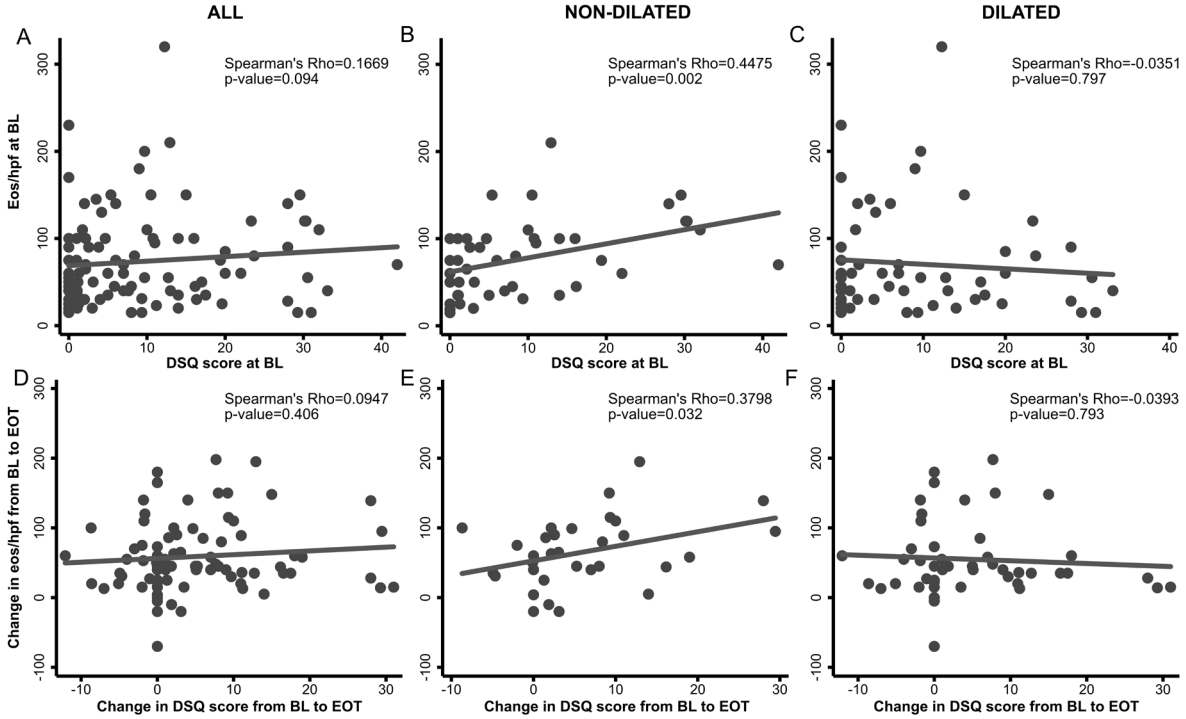

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Figure 2. Relationship between baseline DSQ and EEsAI PRO in all patients (n=73) (**A**), in patients that did not undergo dilation (n=34) (**B**), and in patients that were dilated (n=39) (**C**) at study baseline. Relationship between baseline DSQ 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.

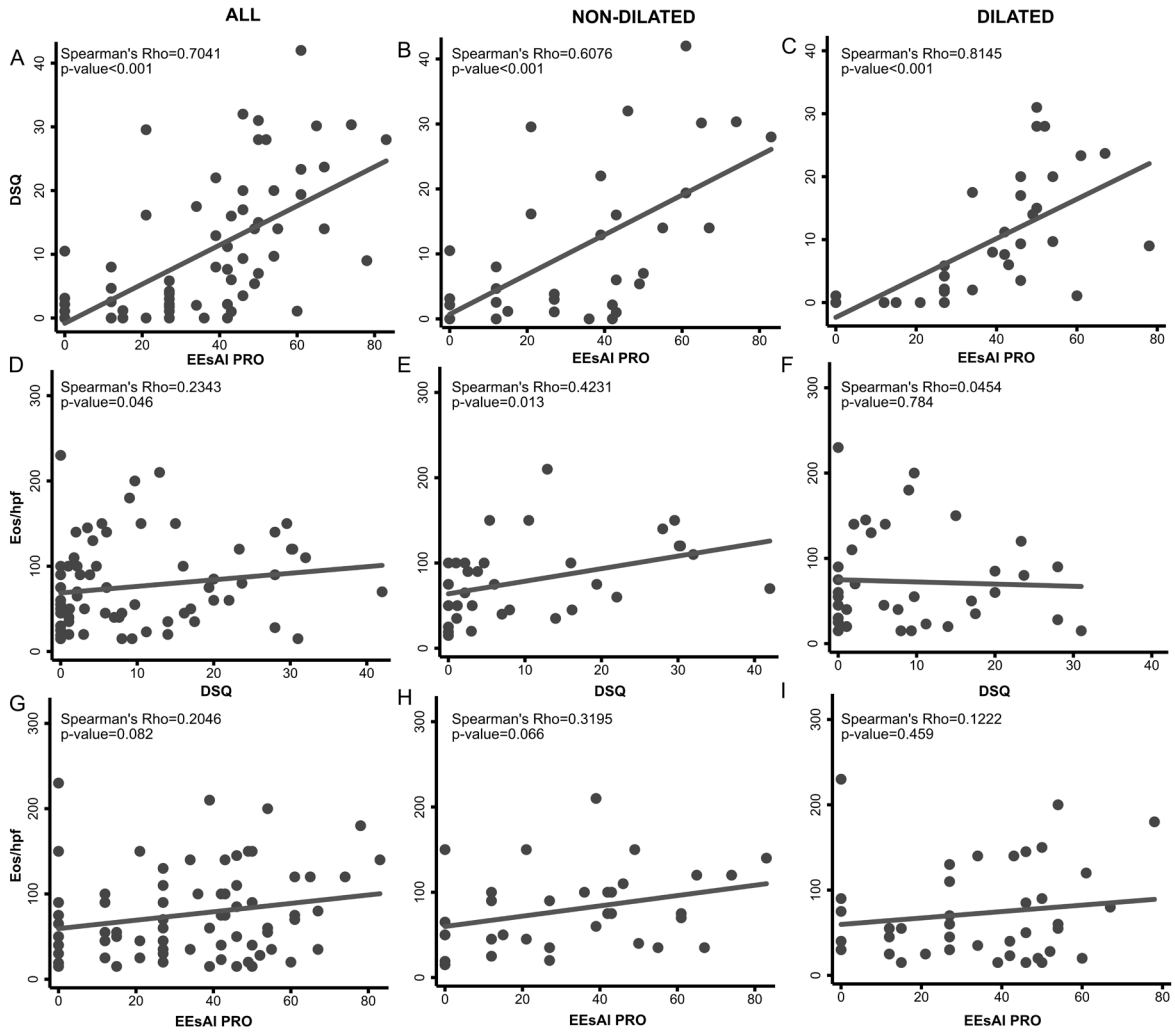
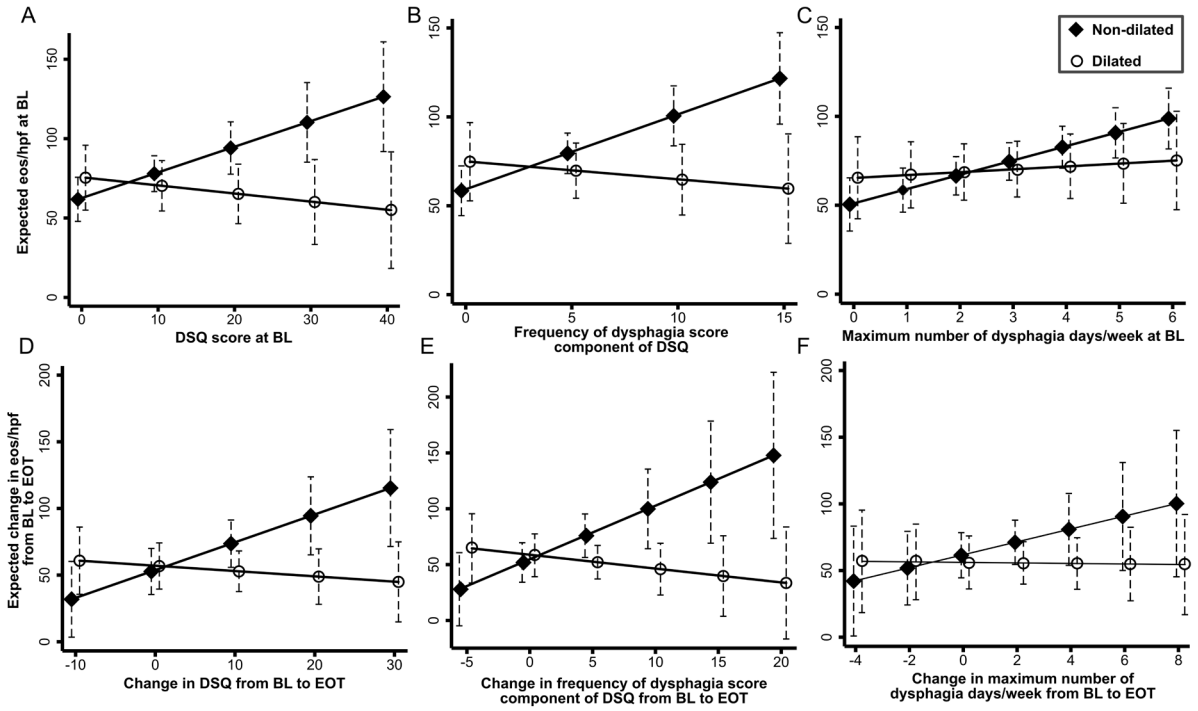


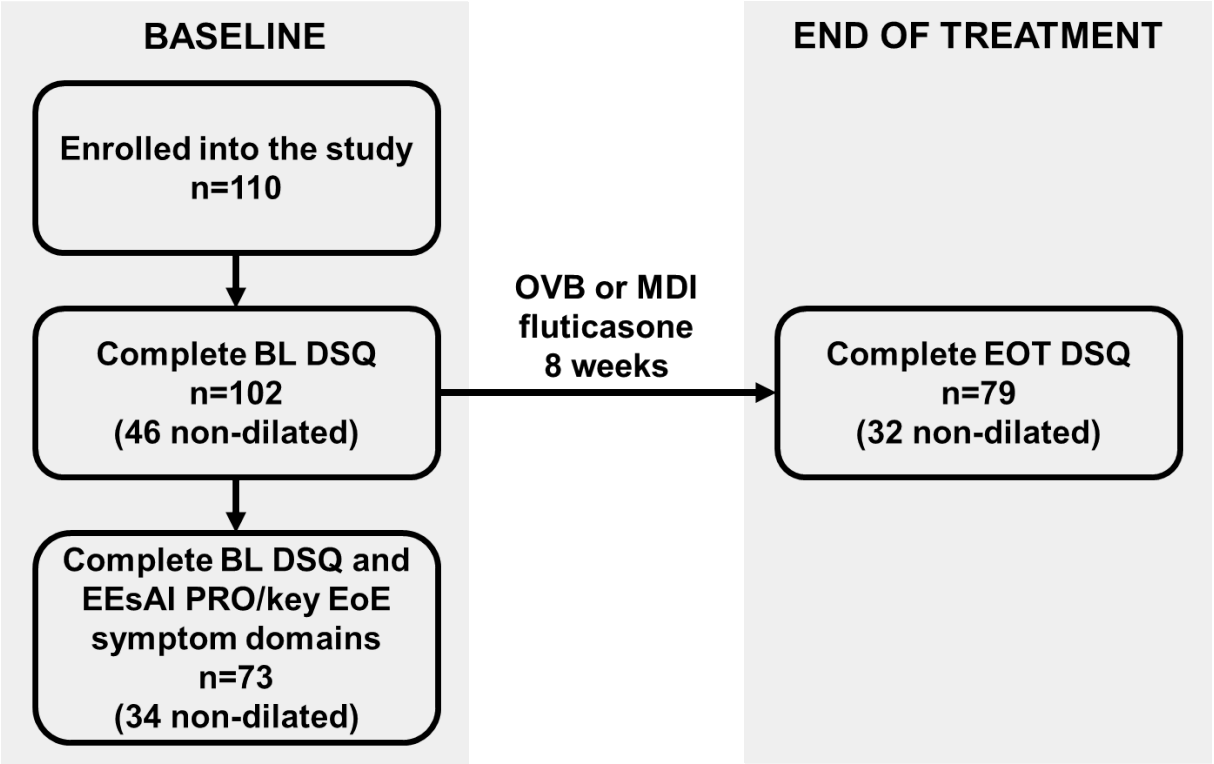
Figure 3. The margin plot of expected esophageal eosinophilia stratified on dilation (n=102) by DSQ (**A**), dysphagia frequency component of DSQ (**B**), and maximum number of dysphagia days per week (**C**) at study baseline. The predictive margins of change from baseline to end of treatment in esophageal 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).



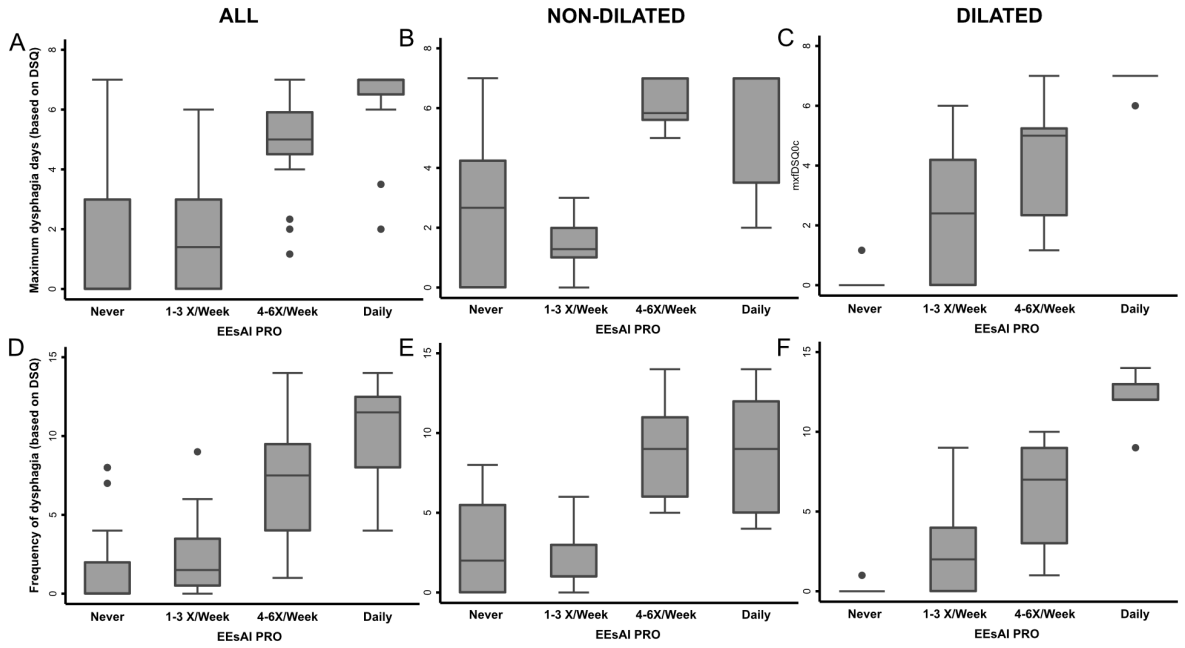
[a] (**A**) in non-dilated patients with the DSQ score of 10 and 30 points, predicted values of 77 eos/hpf and 110 eos/hpf, respectively, are observed (**A**). In dilated patients with the DSQ score of 10 and 30 points, predicted values of 70 eos/hpf and 60 eos/hpf, respectively, are observed.

[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.

Supplementary Figure 1. Flow chart of patient populations. All the patients with complete DSQ (completed for at least 4 days in a seven-day period) and EEsAI PRO subdomains data at baseline and all the patients with complete DSQ at end of treatment were analyzed for the purposes of this study.



Supplementary Figure 2. Relationship between maximum dysphagia days (based on DSQ) and the frequency of the trouble swallowing (EEsAI PRO) (**A-C**), as well as between dysphagia frequency score (DSQ) and the frequency of the trouble swallowing (EEsAI PRO) (**D-F**) features. For each distribution, the box spans the values between the quartiles 1 and 3 (interquartile range), and the median is marked by horizontal line inside the box. The whiskers extend to the maximum of 1.5× the interquartile range beyond the box boundaries. Data beyond the range of whiskers are outliers and presented as points. In the trend test for each panel, p-values ≥ 0.004 or smaller were observed. **Abbreviations:** DSQ, dysphagia symptom score; EEsAI PRO, eosinophilic esophagitis activity index patient-reported outcomes instrument.



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