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Prospective assessment of serum periostin as a biomarker for diagnosis and monitoring of eosinophilic esophagitis

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Summary

Background—Periostin is highly expressed in eosinophilic esophagitis (EoE), but has not been extensively studied as a non-invasive biomarker.

Aim—To assess whether serum periostin distinguished EoE from controls at baseline, had utility for monitoring treatment response, or was associated with IL-13 levels.

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Higgins: patient recruitment and sample collection; data acquisition/management; critical revision

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Methods—This was a sub-analysis of a prospective cohort study of adults undergoing outpatient upper endoscopy. Incident cases of EoE were diagnosed per consensus guidelines. Controls were subjects with either GERD or dysphagia without EoE. EoE patients were treated with swallowed/topical steroids and had repeat endoscopy/biopsy. Serum periostin levels for cases and controls were compared at baseline, and pre/post-treatment levels were compared for cases. Serum IL-13 and tissue expression of periostin were also assessed.

Results—A total of 61 incident EoE cases and 87 controls were analyzed. Despite a marked increase in tissue periostin expression in cases, the median baseline serum periostin level was only slightly higher in cases than controls (22.1 ng/mL vs 20.7; p=0.04); there was no change in post-treatment levels. There was also no difference in serum periostin for cases by histologic response or atopic status. There was a strong trend towards higher serum IL-13 levels in cases in the highest periostin quartile (57.1 pg/mL vs 2.6; p=0.07).

Conclusions—Serum periostin levels were similar in cases and controls, and there were no changes post-treatment. Given elevated IL-13 levels in the EoE patients with the highest periostin levels, future studies could explore periostin as a biomarker in EoE, perhaps in the setting of anti-IL-13 therapy.

Keywords

Eosinophilic esophagitis; periostin; serum biomarker; gene expression; diagnosis; monitoring

Introduction

Eosinophilic esophagitis (EoE) is a clinicopathologic condition characterized clinically by symptoms of esophageal dysfunction and histologically by eosinophilic infiltration of the esophageal mucosa,[1, 2] and the increasing incidence is outpacing recognition.[3] Diagnosis of EoE currently requires an invasive procedure, upper endoscopy with biopsy, to obtain tissue for histologic analysis and quantification of esophageal eosinophil counts.[1, 2] Similarly, after treatment is prescribed, repeat endoscopy is required to monitor disease activity as clinical symptoms do not always correlate with biopsy results.[4–6] Because of this burden of diagnosis and monitoring,[7] non-invasive biomarkers would have a valuable role. While there is intense research in biomarker discovery in EoE, to date results regarding serum,[8–15] saliva,[16] stool,[8, 9] and respiratory[17, 18] biomarkers have been mixed and none are routinely used in clinical care.[19]

Periostin is an extracellular matrix protein that is present in the esophageal epithelium, is highly expressed in patients with EoE, and is induced by IL-13.[20–22] It is thought to facilitate eosinophil tissue infiltration by promoting eosinophil adhesion to fibronectin.[23] Therefore, it may be a promising marker of EoE. With the exception of a clinical trial that assessed serum periostin levels in EoE patients before and after treatment with an anti-IL-13 monoclonal antibody[13] and an abstract assessing a series of EoE cases,[24] serum periostin has not been assessed as a biomarker for either diagnosis or monitoring of EoE. However, there has been experience using periostin levels to direct treatment of asthma with anti-IL-13 medications,[25–27] and assays to measure periostin in serum have now made it possible to examine this issue in depth in EoE.

The aims of this study were to determine the feasibility of measuring serum periostin, assess whether it distinguishes EoE from controls at baseline, investigate its utility for monitoring EoE after treatment, and evaluate associations between periostin and IL-13 levels. We hypothesized that serum periston levels would be higher in EoE cases as compared to non-EoE controls, and that levels would decrease after successful treatment of EoE.

Materials and Methods

Study design and case definitions

This was a sub-analysis of a prospective cohort study conducted at University of North Carolina from July, 2011 through December, 2013. Full details of the study design have been previously described.[28–32] In brief, patients aged 18–80 years who were undergoing outpatient upper endoscopy for evaluation of symptoms of esophageal dysfunction (e.g. dysphagia, food impaction, heartburn, reflux, chest pain) were consecutively enrolled. Informed consent, including consent for future use of stored specimens, was obtained prior to the endoscopy. Exclusion criteria were: a known diagnosis of EoE or a different eosinophilic gastrointestinal disorder (EGID), GI bleeding, active anticoagulation, known esophageal cancer, prior esophageal surgery, known esophageal varices, medical instability or multiple comorbidities precluding enrollment in the clinical opinion of the endoscopist, or inability to read or understand the consent form. This study was approved by the UNC Institutional Review Board and registered on clinicaltrials.gov (NCT 01988285)

EoE cases were diagnosed by consensus guidelines.[1, 2] Cases had to have at least one typical symptom of esophageal dysfunction and ≥15 eosinophils per high-power field (eos/hpf) on esophageal biopsy after an 8 week PPI trial (20–40 mg twice daily of any of the available agents, prescribed at the discretion of the clinician); other causes of esophageal eosinophilia also had to be excluded. Controls were subjects who did not meet clinical or histologic criteria for EoE after endoscopy and biopsy. Subjects with PPI-responsive esophageal eosinophilia (PPI-REE)[33, 34] were not included in this study.

Clinical data and patient follow-up

Demographics, symptoms, concomitant atopic diseases, indications for endoscopy, and endoscopic findings were recorded using a standardized case report form. Research-protocol esophageal biopsies were obtained (two from the proximal, one from the mid, and two from the distal esophagus) to maximize EoE diagnostic sensitivity,[35, 36] and research-protocol gastric and duodenal biopsies were also collected to exclude concomitant eosinophilic gastroenteritis. Additional clinical biopsies could be taken as indicated at the discretion of the endoscopist. The study pathologists quantified the esophageal eosinophil counts using our previously validated technique.[37] Slides were masked to case/control status, digitized, and reviewed with Aperio ImageScope (Aperio Technologies, Vista, CA). Five microscopy fields from each of the five biopsies were examined to determine the maximum eosinophil density (eosinophils/mm^2 [eos/mm^2]). To compare data with prior studies, eosinophil density was converted to an eosinophil count (eos/hpf) using a hpf size of 0.24 mm^2, the most commonly reported field size in the literature.[38]

After diagnosis, patients with confirmed EoE were treated with topical corticosteroids (either oval viscous budesonide 1 mg twice daily or fluticasone from a multi-dose inhaler, 880 mcg twice daily) for 8 weeks as clinically indicated.[39–42] At that time, a repeat upper endoscopy with biopsy was performed.

Serum measures

A blood sample was obtained from all subjects before each procedure and labelled with a unique de-identified study number that was blinded as to case/control and treatment status. The sample was centrifuged and serum aliquots were separated, frozen, and stored at −80°C. After patient enrollment and follow-up were complete, samples were removed from the freezer, arranged in random order, thawed only once, and analyzed in a batch.

Serum periostin was measured by ELISA (AdipoGen, San Diego, CA; AG-45B-0004-KI01). Samples were run in duplicate on 96-well plates with standards and positive/negative controls per manufacturer instructions. IL-13 had previously been measured in the same patients.[28]

Tissue measures

In addition to the biopsy samples obtained for histopathologic assessment, additional biopsy samples were collected, labelled with a de-identified study number, and stored at −80°C in order for future use. Based on our prior study showing that gene expression was similar throughout the esophagus,[32] this study utilized a single RNAlater (Life Technologies/ Thermo-Fisher Scientific, Grand Island, NY) preserved biopsy from the mid esophagus from each subject to determine tissue expression of periostin. RNA extraction was performed on the homogenized specimens using the RNeasy Mini Extraction Kit (Qiagen, Germantown, MD) using standard technique. mRNA expression was quantified by performing TaqMan qPCR amplification for a panel of 94 representative EoE genes and 2 housekeeping genes, as previously described.[32, 43] For the present analysis, only periostin expression (POSTN) was analyzed.

Statistical analysis

Descriptive statistics were calculated for the baseline clinical, endoscopic, and histologic characteristics of the EoE cases and non-EoE controls. The median baseline serum periostin levels were compared between cases and controls using the Wilcoxon Rank-Sum test. For the EoE cases, median baseline and post-treatment periostin levels were compared using the Wilcoxon Signed-rank test. Analyses were also performed after stratification by atopic status (defined as the presence of either asthma, atopic dermatitis, allergic rhinitis/sinusitis, of food allergy) or by histologic response to treatment for the EoE cases (defined as <15 eos/hpf).[4, 5] Receiver operating characteristic curves were constructed and areas under the curve (AUC) were calculated to determine the utility of serum periostin for distinguishing EoE cases from controls at baseline. We divided EoE cases into the lowest and highest quartiles of serum periostin, and compared clinical, endoscopic, and histologic features, as well as serum IL-13 levels, between these groups. We also explored periostin levels by selected clinical, endoscopic, and histologic characteristics. Finally, esophageal POSTN expression levels

were analyzed after normalization to GAPDH expression (POSTN Ct – GAPDH Ct). Analyses were performed with Stata 9.2 (College Station, TX).

Results

Patient characteristics

There were 61 EoE cases and 87 controls included in this study; baseline characteristics of these subjects have been previously described.[28] Compared to controls, cases were younger (39 vs 52 years; p<0.001), had more dysphagia (97 vs 79%; p=0.002), less heartburn (18% vs 68%; p<0.001), and more atopic disorders (74% vs 53%; p=0.01). On endoscopy, typical features of EoE were more common in cases, including rings (74% vs 8%), narrowing (23% vs 2%), linear furrows (87% vs 3%), white plaques or exudates (43% vs 3%), and decreased vascularity or edema (59% vs 3%; p<0.001 for all). Similarly, the mean baseline eosinophil counts were markedly elevated in the cases compared to controls (147 vs 3 eos/hpf; p<0.001).

Baseline and post-treatment periostin levels

At baseline, the EoE cases had a slightly higher median baseline serum periostin level than controls (22.1 ng/mL [IQR 20–26] vs 20.7 [16–24]; p=0.04) (Table 1). However, the AUC was just 0.60 for using this marker for diagnosis of EoE. Serum periostin levels were also similar for cases and controls after stratification by atopic status (Table 1).

A total of 48 EoE cases had paired pre- and post-treatment serum samples that could be analyzed. In this subset, median baseline periostin was 22.6 (IQR 20–27) and after topical steroid treatment it fell slightly to 21.5 (18–3–25.1; p=0.12) (Table 1). Changes were not more pronounced when only examining the 27 histologic responders. In this group, baseline periostin was 23.0 (18–27) and post-treatment the level decreased to 21.3 (18–25; p=0.13).

Periostin, clinical features, and IL-13

Analysis of median baseline serum periostin levels in EoE cases showed that levels overall were similar after stratification by clinical and endoscopic features (Figure 1). However, there were trends towards slightly higher levels in EoE patients with atopy compared to those without atopy (23.3 [IQR 20–27] vs 21.0 [20–22]; p=0.08) and in EoE patients with esophageal narrowing compared to no narrowing (25.0 [23–28] vs 21.8 [20–25]; p=0.11). There were no associations between these levels and clinical features in controls (data not shown).

After dividing the EoE cases into quartiles based on serum periostin levels, there were no major clinical, endoscopic, or histologic differences between those cases in the lowest quartile compared to those in the highest quartile (Table 2). There was a possible trend towards an increased symptom duration prior to diagnosis in the high periostin group (69% vs 43%) but this was not significant (p=0.25). However, there was a strong trend towards higher median IL-13 levels in the highest quartile of EoE cases compared to the lowest quartile (57.1 pg/mL [IQR 1–132] vs 2.6 [0–47]; p=0.07). Additionally, in the cases with the highest periostin levels, there were some minor differences in periostin after treatment. For

the histologic responders (n = 11), median baseline serum periostin was 28.9 ng/mL (IQR: 27.4–30.9) and this decreased to 24.9 (23.4–28.2) after treatment (p = 0.07). For the non-responders (n = 5), median baseline serum periostin was 29.3 (28.3–32.2) and decreased to 26.8 (23.8–29.5) after treatment (p = 0.04).

Esophageal POSTN expression

Given the few differences seen in serum periostin levels, we assessed mRNA expression of POSTN in our cases and controls; samples were available for 80 controls and 57 cases. Esophageal POSTN expression was markedly elevated in the EoE cases at baseline compared to controls, and decreased significantly post-treatment (Figure 2). Post-treatment expression was also lower in histologic responders compared to histologic non-responders. The correlation between baseline tissue POSTN and the baseline tissue eosinophil count was good (Spearman's Rho=0.69; p<0.001). In addition, median serum IL-13 levels were higher in the EoE cases in the highest quartile of tissue POSTN expression compared to cases in the lowest quartile (64.2 pg/mL [IQR 4–151] vs 0.3 [0–37]; p=0.04).

Discussion

Given the burden of invasive testing with endoscopy and biopsy for diagnosis and monitoring of EoE, a non-invasive biomarker-based blood test would be of immense value. In this study, we analyzed the potential for serum periostin to fill this role. Periostin is one of the most highly upregulated genes in the EoE transcriptome[20] and is involved in EoE pathogenesis by promoting adherence of eosinophils to fibronectin in the esophageal mucosa.[23] Periostin is also induced by IL-13[22, 23] and is more highly expressed in the absence of desmoglein-1.[44] Therefore, it seemed to be a promising option. While we were readily able to measure serum periostin, found that baseline levels were slightly higher in EoE cases than controls at baseline, and observed slightly lower levels in EoE cases after treatment, these changes were not large enough to have clinical utility for either EoE diagnosis or monitoring of therapy. This conclusion was determined despite demonstrating markedly elevated tissue expression of POSTN in EoE cases. We also did not see any clear relation between serum periostin and clinical phenotype. However, we did see d that serum IL-13 levels were higher in the EoE cases with the highest levels of serum periostin and tissue POSTN expression.

To our knowledge, only one prior study and one abstract examined serum periostin in EoE. In the abstract, serum periostin levels in 23 EoE cases were quite high (mean 187 ng/mL), but the results cannot be directly compared with ours because they reported means and used a different ELISA assay; controls were not assessed.[24] The other study was a randomized clinical trial where 17 patients received an anti-IL-13 treatment and 8 received placebo.[13] At baseline, the mean periostin levels were approximately 91 ng/mL in the treatment group and 80 ng/mL in the placebo group, and a modest but non-significant decrease was observed after treatment. However, the levels in this study may not be directly comparable to the levels in our study, as the investigators used liquid chromatography-mass spectrometry and report means, whereas we used a commercially available ELISA and report medians. The investigators also saw that subjects with serum periostin levels above the median had a

higher histologic response rate, a finding that we did not observe, though their treatment was with an anti-IL-13 antibody and ours was with a topical corticosteroid. This lack of change in the serum is in contrast to what we and others have observed with tissue expression of periostin, where high levels of baseline expression markedly decrease after treatment.[13, 23, 45, 46] Interestingly, we did observe that patients with the highest periostin serum and tissue levels also had high levels of IL-13. This is an important confirmation in vivo in humans of what has previously been noted in cell lines and animal models.[22, 23]

While it is possible that serum levels of periostin patients in EoE do not reflect its increased esophageal expression, the experience with periostin in asthma might argue against this. Several studies,[25–27, 47] though not all,[48] suggest that in asthma serum periostin levels tend to correlate with severity of airway inflammation,[25] and patients with periostin levels above the median for the study population have a better response to anti-IL-13 medications.[26, 27, 47] Some of these studies found median periostin levels in the same range as in our study (20–25 ng/mL),[25, 47] but others noted higher levels (50 ng/mL).[26] The discrepancy between the results in asthma and in EoE will require additional study to fully determine the utility of serum periostin in EoE.

There are several limitations of this study to consider. First, it was conducted at a single referral center, and the design would have been stronger if this were done as part of a clinical trial. However, the EoE patients seen at our site tend to have similar characteristics to other populations reported in the literature. Second, because this was a negative study, we cannot exclude the possibility of a type II error. However, this was a large sample of patients and the parent study was appropriately powered to assess biomarker measures.[28] While it is possible that errors in sampling handling could explain negative results, all samples were collected, processed, and handled identically and there is no clear reason that degradation of samples would be differential between cases and controls. The ELISA assay we used is also likely not a cause. Though newly commercially available, the range of our serum periostin levels were roughly on the same order of magnitude than what has been previously reported in EoE and asthma;[13, 47] however we cannot exclude a measurement different given the recent data presented in abstract form using a different ELISA.[24] There are also several strengths of this study that lend validity to the results. We analyzed a large number of EoE cases and clinically relevant controls. Samples were prospectively collected using rigorous methodology, stored at −80°C, and only thawed once for the present analysis. Identical collection procedures were used for the follow-up samples. The EoE cases were a highly inflamed population, with demonstrated tissue elevation of periostin expression, so this study should have provided an optimal setting in which to detect differences in serum periostin.

In conclusion, in this study of a large number of prospectively collected samples from EoE cases and non-EoE controls, we were readily able to measure serum periostin using a commercially available assay. While we observed slightly higher baseline levels of serum periostin in EoE cases than in controls, there was no change in periostin after treatment with a topical corticosteroid, and overall the differences in serum periostin were not clinically meaningful. We also did not detect differences by atopic status or histologic response. However, we did find that IL-13 levels were highest in the EoE patients with the highest

quartile of both serum periostin levels and tissue POSTN expression. Given this observation, as well as the increasing data on the use of periostin to stratify asthma treatment with biologic therapies such as anti-IL-13 antibodies, further studies should explore the potential of periostin as a biomarker in similar treatment settings in EoE.

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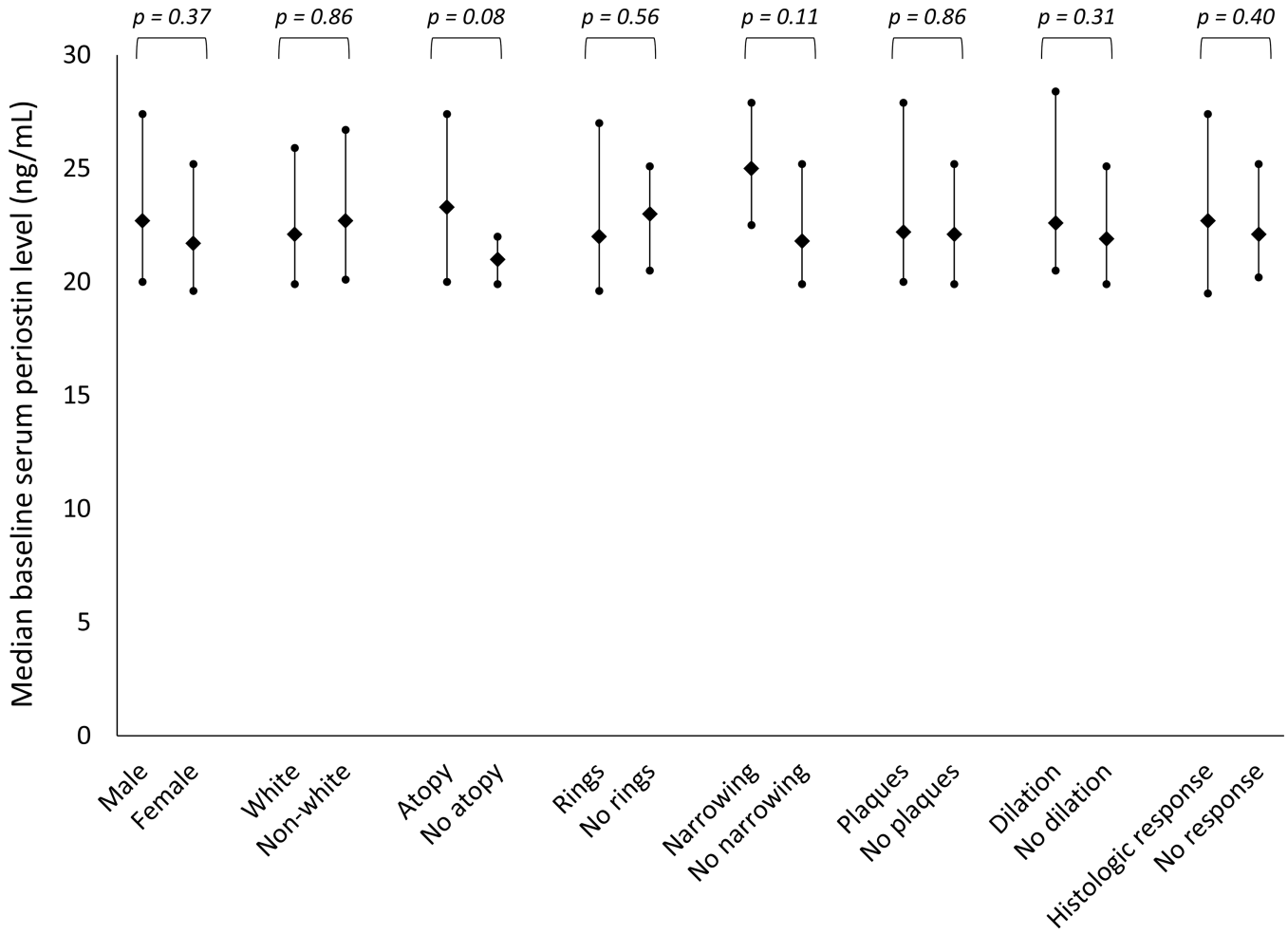

Figure 1.

Median periostin levels, as indicated by the diamond, for selected clinical, endoscopic, and histologic features in EoE cases. Interquartile ranges are noted by the dots at the end of the lines. All comparisons are by Wilcoxon Rank-sum.

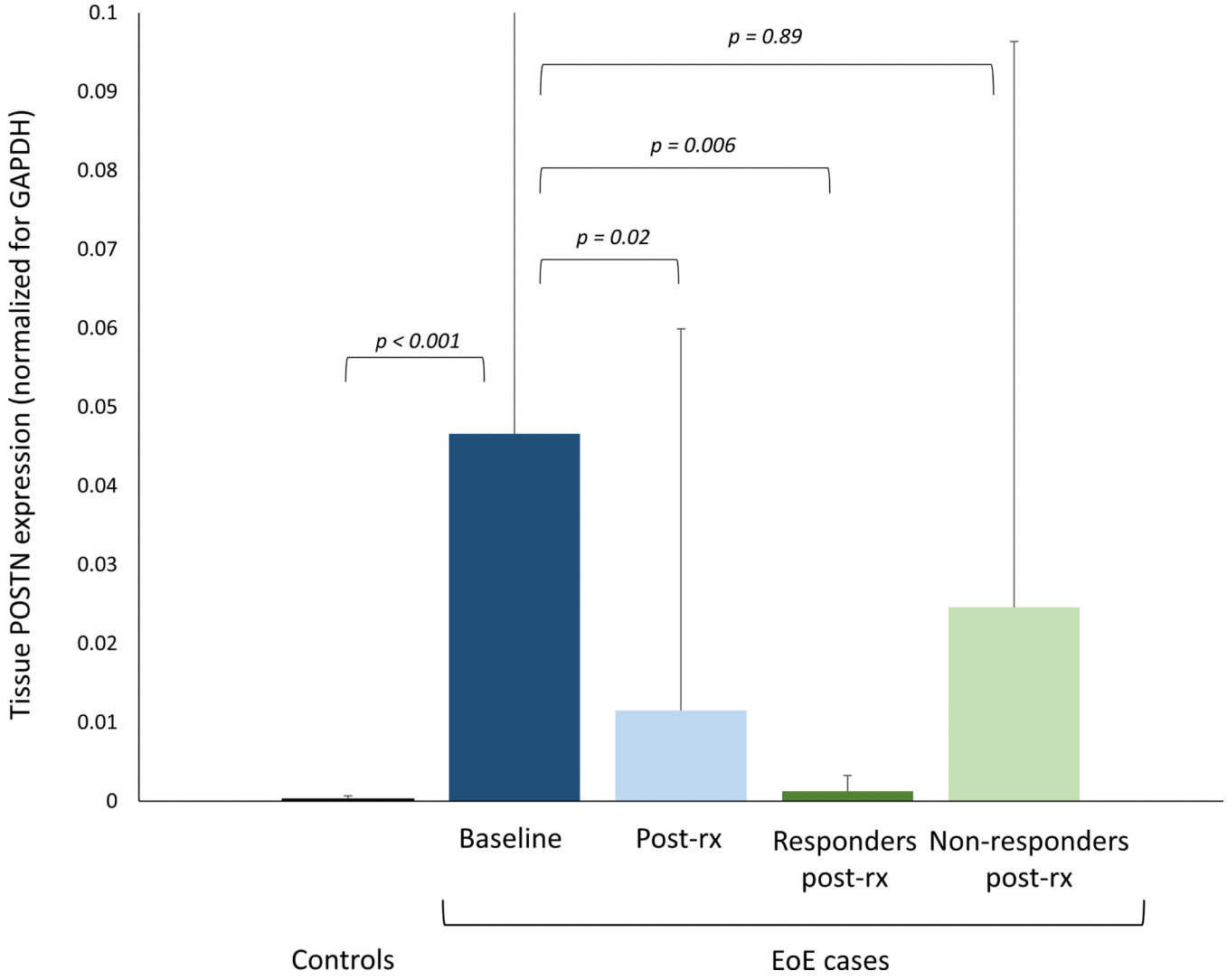

Figure 2.

Tissue expression of POSTN. The GAPDH-normalized relative expression is presented on the y axis for controls (n = 80; black bar) and cases (n = 57; dark blue bar) at baseline, for all cases after treatment (n = 57; light blue bar), and for cases after treatment stratified by histologic response (<15 eos/hpf) status (n = 31 responders; dark green bar; and n = 25 non-responders; light green bar). Unpaired comparisons are by Wilcoxon Rank-sum, and paired comparisons are by Wilcoxon Signed-rank.

Table 1

Serum periostin levels for cases and controls, by treatment response, and by atopic status

	Median periostin level (ng/mL; IQR)
Case-control analysis at baseline	
EoE cases (n = 61)	22.1 (20.0–25.9)
Controls (n = 87)	20.7 (17.5–23.8)
p value *	0.04
Treatment response for EoE cases (n = 48)	
Baseline	22.6 (19.6–26.7)
Post-treatment	21.5 (18.3–25.1)
p value †	0.12
For histologic responders among EoE cases (n = 27)‡	
Baseline	23.0 (18.4–27.4)
Post-treatment	21.3 (18.0–25.1)
p value †	0.13
For cases and controls with atopy#	
EoE cases (n = 45)	23.3 (20.0–27.4)
Controls (n = 46)	21.5 (17.7–23.7)
p value *	0.08

*Calculated with Wilcoxon Rank-sum.

†Calculated with Wilcoxon Signed-rank.

‡Histologic response defined as <15 eos/hpf after treatment.

#Atopy defined as the presence of asthma, allergic rhinitis/sinusitis, atopic dermatitis, or self-reported food allergies/sensitivities.

Table 2

Baseline characteristics of EoE cases stratified by lowest vs highest quartile of serum periostin

	Low periostin (n = 16)	High periostin (n = 16)	p*
Periostin level (median ng/mL; IQR)	17.4 (15.8–16.6)	29.1 (27.7–31.4)	--
Age (mean years ± SD)	38.6 ± 13.1	37.9 ± 12.7	0.87
Male (n, %)	8 (50)	3 (31)	0.47
White (n, %)	15 (94)	15 (94)	1.0
Symptoms (n, %)			
Dysphagia	16 (100)	16 (100)	--
Symptom duration > 5 years†	6 (43)	9 (69)	0.25
Heartburn	2 (13)	4 (25)	0.65
Abdominal pain	4 (25)	2 (13)	0.65
Any atopic disease (n, %)	12 (75)	15 (94)	0.33
Asthma	4 (25)	6 (38)	0.70
Rhinitis/sinusitis	11 (69)	14 (88)	0.39
Dermatitis	1 (6)	1 (6)	1.0
Food allergies	7 (44)	12 (75)	0.15
Endoscopic findings (n, %)			
Normal	1 (6)	0 (0)	1.0
Rings	13 (81)	13 (81)	1.0
Stricture	3 (19)	4 (25)	1.0
Narrowing	3 (19)	6 (38)	0.43
Furrows	15 (94)	14 (88)	1.0
Crêpe-paper mucosa	0 (0)	3 (18)	0.23
White plaques/exudates	7 (44)	9 (56)	0.72
Edema/decreased vascularity	9 (56)	11 (69)	0.72
Dilation performed	4 (25)	7 (44)	0.46
Eosinophil count (max eos/hpf ± SD)			
Baseline	133.4 ± 78.6	172.7 ± 156.0	0.37
Post-treatment	23.8 ± 43.9	36.4 ± 81.8	0.59
Treatment response (n, %)‡	11 (69)	11 (69)	1.0
Baseline IL-13 (median pg/mL; IQR)#	2.6 (0–46.7)	57.1 (1.4–132.1)	0.07

*Fisher's exact used for proportions, t-test used for means, Wilcoxon Rank-sum used for medians.

†Data available for n = 27.

‡Histologic response defined as <15 eos/hpf after treatment.

#Data available for n = 31