

Periostin as a Biomarker for Nasal Polyps in Chronic Rhinosinusitis

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Abstract

Objective. Periostin is an extracellular matrix protein that is elevated in the sinonasal tissues of patients with chronic rhinosinusitis (CRS). The purpose of this study was to determine whether serum periostin could serve as a molecular biomarker of nasal polyp burden in sinonasal disease.

Study Design. Prospective cohort study.

Setting. Academic medical center.

Subjects and Methods. Serum periostin levels were measured by ELISA on blood samples collected from patients undergoing sinus surgery for CRS (n = 71), further stratified by phenotype as defined by nasal polyps and asthma. Results were compared with assays performed on control subjects (n = 62).

Results. Mean serum periostin levels were markedly elevated in patients with CRS versus controls (66.1 ng/mL [95% CI, 51.6–80.6] vs 38.7 ng/mL [95% CI, 34.4–42.9], respectively, $P = .004$). In addition, mean periostin levels were significantly higher in CRS patients with nasal polyps as compared with those without polyps (94.8 ng/mL [95% CI, 67.3–122.4] vs 41.1 ng/mL [95% CI, 35.2–47.0], respectively, $P < .001$). Periostin levels did not correlate with sex ($P = .473$), smoking history ($P = .748$), aspirin-exacerbated respiratory disease status ($P = .136$), oral steroid use within 1 month of surgery ($P = .281$), use of topical steroid nasal spray ($P = .864$), or number of prior sinus operations ($P = .973$).

Conclusion. Serum periostin appears to be a novel molecular biomarker for the presence of nasal polyps and may serve as an indicator of CRS endotypes.

Keywords

periostin, chronic rhinosinusitis, nasal polyps, asthma, biomarker, phenotype, endotype

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Nasal polyp formation in chronic rhinosinusitis (CRS) is associated with an upregulation in the Th-2 immune response, which includes the cytokines interleukin 4 (IL-4), IL-5, and IL-13.^{1–3} Specifically, IL-4 and IL-13 induce the production of periostin, a 90-kDa extracellular matrix protein secreted by fibroblasts.^{1,2,4,5} Periostin (encoded by the gene *POSTN*) interacts with integrin molecules on cell surfaces, providing signals for tissue development and remodeling.^{5,6} Because of its interaction in cell signaling pathways, periostin has been assigned to a class of matrix proteins known as matricellular proteins.⁷

Periostin is a mediator of fibrosis that has been implicated in various pathologic processes, including pulmonary and cardiac disease.^{6,8–11} In patients with bronchial asthma, periostin is produced by lung fibroblasts and deposited in the basement membrane of respiratory epithelium.^{2,3,12} High levels of periostin have been associated with a poor response to inhaled corticosteroid therapy, making it a useful biomarker in the prediction of treatment responsiveness in select patients with asthma.^{3,13–15} Clinical studies have also demonstrated increased expression of periostin in myocardial tissue in response to cardiac stress, leading to cardiac remodeling and fibrosis seen after myocardial infarction.^{10,16} Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are used to prevent postinfarction cardiac remodeling through inhibition of the renin-angiotensin system, the inhibition of which has been correlated with decreased periostin expression.^{10,17}

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Our genome-wide transcription study showed periostin expression to be markedly upregulated in nasal polyps as compared with normal sinus mucosa.¹⁸ This finding was confirmed by real-time quantitative reverse transcription polymerase chain reaction and immunohistochemistry.¹⁸ In a recent study by Brook et al, we found that the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with nasal polyps and asthma significantly delayed the time to revision sinus surgery by >2 years, suggesting a possible mechanism by which polyp formation can be influenced through inhibition of periostin expression.¹⁹ Given these findings, we sought to explore the role of periostin expression in the development of nasal polyps. The purpose of the current study was to measure serum periostin levels in patients with sinonasal disease and controls to determine the applicability of periostin as a potential molecular biomarker for CRS and its endotypes.

Methods

Study Design

Study patients were enrolled prospectively. All subjects in the disease cohort had a diagnosis of CRS and were scheduled to undergo sinus surgery. Blood samples were collected at the time of surgery. Exclusion criteria included age <18 years or a history of inverted papilloma, cystic fibrosis, or sinonasal granulomatous disease. Demographic and clinical information was obtained from the patient and medical records and included age, sex, smoking status, asthma, aspirin-exacerbated respiratory disease status, oral steroid use within 1 month of surgery, usage of topical steroid nasal spray, and number of previous endoscopic sinus operations. The presence of polyps was determined by the preoperative endoscopic nasal examination and findings at time of surgery, which was performed between October 2015 and October 2016.

The control group comprised 2 cohorts. The first encompassed surgical patients undergoing endoscopic nasal surgery for a diagnosis other than CRS, including septoplasty, orbital decompression, and dacryocystorhinostomy. The second was composed of de-identified blood samples from healthy individuals who had been approved for donation at the hospital's blood donor center. Age and sex were the only known demographics in this latter group. Institutional Review Board approval was given by the Human Studies Committee of the Massachusetts Eye and Ear Infirmary (04-07-043).

Measurement of Serum Periostin Level

Whole blood samples collected in the operating room were centrifuged at 4136 $\times g$ (BEAR BC-400R; Thomas Scientific, Swedesboro, New Jersey). Serum samples were aliquoted, frozen at -80°C , and thawed immediately before use.

Serum periostin levels were measured by enzyme-linked immunosorbent assay (ELISA) with the DuoSet ELISA Kit (human periostin/OSF-2 DuoSet ELISA; R&D Systems, Minneapolis, Minnesota). ELISAs were performed in 96-

well polystyrene plates prepped with capture antibody incubated overnight. The following day, the plate was washed and blocked with reagent diluent and incubated for a minimum of 1 hour. The samples were diluted by a factor of 50, and 100 μL of the diluted sample was added to each well, with duplicate samples, and incubated for 2 hours. The plate was then washed again, followed by addition of detection antibody, and incubated for 2 hours. The wash was repeated after each incubation period. Streptavidin–horseradish peroxidase was added to bind to the detection antibody. A substrate solution was added and converted by the enzyme to a detectable color signal. Stop solution was added to each well after 20 minutes. The different absorbances at the wavelengths 450 and 570 nm were evaluated after the addition of the stop solution.

Statistical Analysis

An a priori sample size calculation was performed prior to recruitment, based on findings of periostin levels in healthy subjects and patients with asthma. Our sample size calculation estimated that 21 patients would be needed in each of the control and diseased groups ($\alpha = 0.05$, power 80%) to detect a statistically significant difference. Recruitment for the present study was allowed to surpass this estimated sample size value, as the mean and variance in the level of periostin in patients with CRS were unknown prior to this study. Statistical analysis was performed with the R Project for Statistical Computing (version 3.2.5; R Foundation for Statistical Computing, Vienna, Austria).²⁰ Wilcoxon-Mann-Whitney analysis, analysis of variance, and the Kruskal-Wallis procedure were used to compare serum periostin levels among groups. The Benjamini-Hochberg procedure for multiple comparisons was applied. A multivariate regression model was used to examine the associations of each variable with periostin level.

Results

The study population was comprised of 133 patients, whose demographics are shown in **Table 1**. The CRS group included 33 patients with a diagnosis of CRS with nasal polyps (CRSwNP) and 38 patients with CRS without nasal polyps (CRSsNP). The mean periostin level in the total CRS group was 66.1 ng/mL (95% CI, 51.6–80.6), as compared with 38.7 ng/mL (95% CI, 34.4–42.9) in the control group ($P = .004$). The CRSwNP cohort had the highest mean, 94.8 ng/mL (95% CI, 67.3–122.4), whereas a mean of 41.1 ng/mL (95% CI, 35.2–47.0) was observed for those with CRSsNP ($P < .001$), as shown in **Figure 1** and **Table 2**.

Multivariate regression analysis demonstrated that the presence of nasal polyps was an independent predictor of periostin level (parameter estimate = 38.66; 95% CI, 9.23–68.09; $P = .011$). The presence of polyps increased the mean periostin level by 53.2 ng/mL when other factors were not adjusted for, and it increased the mean periostin level by 38.7 ng/mL in the multivariate regression model. Multivariate regression analysis did not demonstrate an association between periostin level and the other studied

Table 1. Patient Demographics.^a

Variables	CRS Total	CRSwNP	CRSsNP	Control	P Value
Patients	71	33	38	62	
Age, y, mean $\pm$ SD	51.9 $\pm$ 15.2	51.4 $\pm$ 14.3	52.4 $\pm$ 16.2	44.3 $\pm$ 17.6	.02 ^b
Sex					
Male	42 (59.2)	23 (69.7)	19 (50.0)	30 (48.4)	.12
Female	29 (40.8)	10 (30.3)	19 (50.0)	32 (51.6)	
Smoking status					
Yes	2 (2.8)	1 (3.0)	1 (2.6)	2 (10.5) ^c	.42
No	69 (97.2)	32 (97.0)	37 (97.4)	17 (89.5) ^c	
Asthma					
Yes	34 (47.9)	22 (66.7)	12 (31.6)	1 (5.3) ^c	<.001 ^b
No	37 (52.1)	11 (33.3)	26 (68.4)	18 (94.7) ^c	
AERD					
Yes	8 (11.3)	8 (24.2)	0 (0.0)	0 (0.0) ^c	<.001 ^b
No	63 (88.7)	25 (75.8)	38 (100.0)	19 (100.0) ^c	

Abbreviations: AERD, aspirin-exacerbated respiratory disease; CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps.

^aValues are presented as n (%) unless noted otherwise.

^b $P < .05$.

^cDenotes only surgical control data.

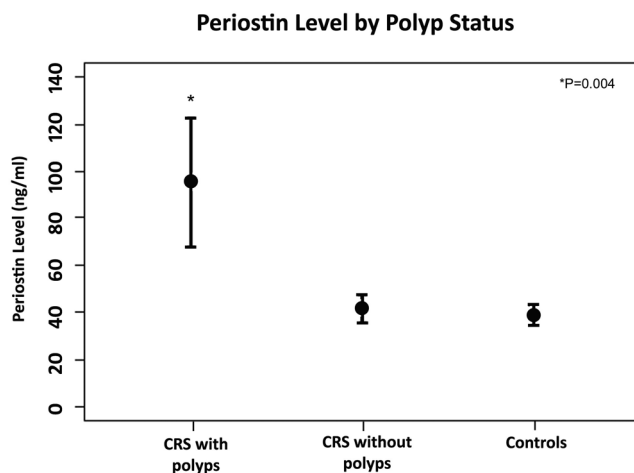


Figure 1. Periostin level by nasal polyp status. Serum periostin level was significantly higher in patients with chronic rhinosinusitis (CRS) and nasal polyps versus patients with CRS without nasal polyps and controls ($P = .004$). Values are presented as means (95% CI).

parameters, including sex ($P = .473$), smoking ($P = .748$), aspirin-exacerbated respiratory disease status ($P = .136$), oral steroid use within 1 month of surgery ($P = .281$), topical steroid nasal spray usage ($P = .864$), or number of previous sinus operations ($P = .973$). The multivariate regression analysis was conducted with the CRS group ($n = 71$) and the surgical controls ($n = 19$) because the anonymous blood donor controls lacked the medical history needed for inclusion in multivariate regression.

Asthma status alone was associated with periostin level ($P = .001$); however, when nasal polyp status was controlled

for with multivariate analysis, this significance was lost ($P = .094$), as shown in **Figure 2**. Patients with CRSwNP and asthma had a mean periostin level of 107.8 ng/mL (95% CI, 69.2-146.4) when compared with patients with CRSwNP and no asthma, who were found to have a mean periostin level of 69.0 ng/mL (95% CI, 43.7-94.4; $P = .110$). Patients with CRSsNP with and without asthma had mean periostin levels of 48.3 ng/mL (95% CI, 35.2-61.5) and 37.8 ng/mL (95% CI, 31.9-43.7; $P = .190$), respectively (**Table 2**).

The 2 cohorts that composed the control group—surgical patients ($n = 19$) without sinus disease and blood donors ($n = 43$)—were found to have similar mean periostin levels (42.8 ng/mL [95% CI, 34.4-51.3] vs 36.8 ng/mL [95% CI, 32.0-41.7], respectively, $P > .990$). The blood donor control group was significantly younger than the surgical control group and the CRS group (mean years: 41.2 vs 51.2 vs 51.9, respectively, $P = .003$).

Discussion

CRS represents a heterogeneous disease process with wide genotypic and phenotypic variation. Currently described clinical CRS subtypes are based on phenotype and are dependent on subjective clinical parameters, such as the presence or absence of nasal polyps, which are both time and observer dependent. These classifications do not reflect the disease's underlying molecular mechanism and therefore are not sufficiently specific for many clinical and research applications.^{21,22} CRS endotyping with molecular biomarkers has the potential to provide a more objective and meaningful system of CRS classification.²³

In the current study, serum periostin level had a strong association with the presence of nasal polyps in patients with CRS. The CRS cohort with polyps had a mean serum

Table 2. Periostin Levels.

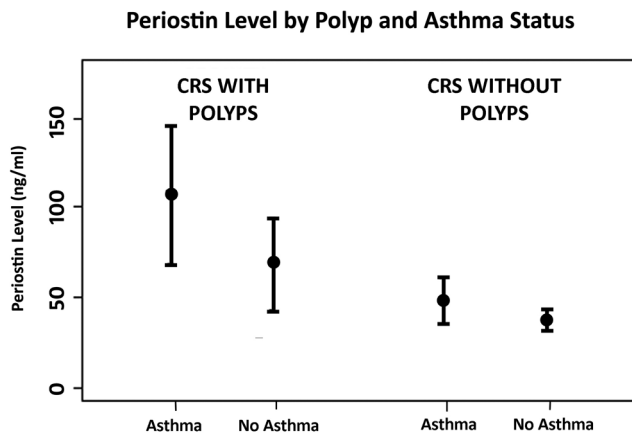
Groups	n	Mean Periostin, ng/mL	95% CI	Range	P Value
CRS total					
Asthma	34	86.8	59.8-113.8	22.0-364.4	<.004 ^a
No asthma	37	47.1	37.5-56.7	12.8-180.3	
Total	71	66.1	51.6-80.6	—	
CRSwNP					
Asthma	22	107.8	69.2-146.4	22.0-364.4	<.001 ^b
No asthma	11	69.0	43.7-94.4	26.8-180.3	
Total	33	94.8	67.3-122.4	—	
CRSsNP					
Asthma	12	48.3	35.2-61.5	24.1-110.4	.79 ^c
No asthma	26	37.8	31.9-43.7	12.8-82.0	
Total	38	41.1	35.2-47.0	—	
Control: total	62	38.7	34.4-42.9	7.0-89.2	

Abbreviations: CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps.

^aCRS total vs control.

^bCRSwNP vs CRSsNP.

^cCRSsNP vs control.

**Figure 2.** Periostin levels by nasal polyp and asthma status.

Although mean serum periostin levels were higher for patients with asthma in both groups—chronic rhinosinusitis (CRS) with and without nasal polyps—this difference was not significant. Values are presented as means (95% CI).

periostin level more than twice as high as those without. Furthermore, patients with CRS without polyp disease had a mean periostin level similar to that of controls. These findings suggest that serum periostin level can be used as a molecular biomarker to stratify CRS into at least 2 distinct molecular endotypes.

The results of the current study indicate that periostin may be a clinically useful biomarker of polyp burden in sinonasal disease. This molecular marker appears to reflect the underlying Th-2 inflammatory response associated with eosinophilia, asthma morbidity, and polyp formation.²⁴ If such a correlation were to be the case, high and low periostin levels (eg, >50 or <50 ng/mL) could serve as a more objective means of determining CRS with endotype rather

than the current phenotypic classification system of CRSwNP and CRSsNP.^{7,23}

The utility of periostin as a biomarker for endotypic classification of airway disease has been described in the pulmonary literature. Woodruff et al used microarray analysis to identify “Th2-high” and “Th2-low” asthma subgroups based on expression levels of periostin and other Th2-driven genes.²⁵ A trial of inhaled corticosteroids resulted in improved lung function only in the patient cohort with Th2-high asthma.²⁵ In a study of 224 patients with asthma, Kanemitsu et al found that a high serum periostin level was a significant risk factor for decline in pulmonary function.²⁶ Furthermore, Matsusaka et al divided patients with asthma based on serum periostin levels and found a correlation between high periostin concentration and nasal disorders, such as CRSwNP and olfactory dysfunction.¹⁴ These findings support the concept of a unified airway theory and suggest the possibility that “periostin-high” and “periostin-low” subgroups may have future diagnostic and therapeutic applicability for patients with CRS.²⁷

The highest periostin levels observed in this study were found in patients with nasal polyps and asthma. Nevertheless, the presence of asthma was not found to be an independent predictor of periostin level, as was the presence of polyps. It is possible that a larger sample size would show such a relationship. On univariable analysis, asthma had a significant association with periostin level, but this effect lost statistical significance after controlling for patients’ polyp status. In addition, none of the other studied parameters correlated with serum periostin level—including smoking status, number of previous endoscopic sinus operations, oral steroid use within 1 month of surgery, and topical steroid usage.

Periostin may serve as a surrogate marker of Th2-driven inflammation in the sinonasal passages. In a study of bronchial epithelial brushings, Woodruff et al identified *POSTN*

and 2 additional Th2-driven genes—*CLCA1* and *SERPINB2*—to be induced in patients with asthma.²⁵ In a microarray study of gene expression in patients with CRS, Stankovic et al found 2 genes—*POSTN* and *MET*—to be markedly upregulated in polyp tissue, as compared with normal sinus mucosa, while 2 other genes—*PIP* and *ZAG*—were downregulated.⁶ It is likely that the upregulation of periostin production found in this study represents but 1 component of a gene expression signature that will allow for elucidation of a variety of CRS endotypes.

Because molecular biomarkers such as periostin may reflect underlying pathologic mechanisms of disease, they may serve as novel therapeutic targets. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, given primarily for their antihypertensive and cardioprotective effects, have been shown to reduce expression of periostin and have been linked to delayed polyp regrowth.^{17,19,28} We hypothesize that these observed effects reflect inhibition of periostin production by these agents, which may lead to the slowing of polyp formation. Other potential biomarkers and therapeutic targets have been described for CRS, including p-glycoprotein targeted by verapamil,²⁹ cysteinyl leukotriene targeted by leukotriene receptor antagonists,³⁰ circulating IgE targeted by omalizumab,³¹ and IL-5 targeted by mepolizumab.³²

The results of this study should be interpreted within the context of its limitations. There was a relatively small sample size within each group. The diagnosis of asthma was determined by patient history rather than by objective testing, so asthma severity and treatment history could not be included in the analysis. An interaction variable between asthma and nasal polyps was included in the linear regression model to assess the interactive effect between these 2 parameters and periostin level; however, it was insignificant, likely secondary to the small sample size. It is quite possible that the influence of polyps on periostin level is much greater and thus overshadows that of asthma in the present study and that the independent effect of asthma would likely be demonstrated with a larger sample size. Furthermore, the medical history of the blood donor controls was unknown, so the presence of sinonasal pathology in this group could not be excluded. In future studies, it would be preferable to stratify patients according to asthma severity and steroid-based medication usage to assess the relationship among nasal polyps, asthma status, steroid use, and periostin level. Additionally, studies of larger sample size are needed to determine the relationship between periostin levels and CRS disease severity and patient symptomatology.

Conclusion

A high serum level of periostin, a matricellular protein associated with upper and lower airway disease, is strongly associated with the presence of nasal polyps in patients with CRS. Periostin appears to be a molecular biomarker for CRS variants and may serve as a novel target for future therapeutic interventions.

Author Contributions

Alice Z. Maxfield, study design, acquisition of data, analysis, drafting and revision of the manuscript, final approval; **Lukas D. Landegger**, study design, acquisition of data, analysis, revision of the manuscript, final approval; **Christopher D. Brook**, acquisition of data, revision of the manuscript, final approval; **Ashton E. Lehmann**, acquisition of data, revision of the manuscript, final approval; **Adam P. Campbell**, acquisition of data, revision of the manuscript, final approval; **Regan W. Bergmark**, acquisition of data, revision of the manuscript, final approval; **Konstantina M. Stankovic**, study design, analysis, revision of the manuscript, final approval; **Ralph Metson**, study design, acquisition of data, analysis, drafting and revision of the manuscript, final approval.

Disclosures

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