

Association of airway wall thickness with serum periostin in steroid-naïve asthma

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ABSTRACT

Background: Periostin may be a useful biomarker of T-helper type 2 eosinophilic airway inflammation and has been linked to remodeling in asthma. However, the association between serum periostin and the magnitude of airway wall thickness remains unclear.

Objective: We examined the relationship between serum periostin and airway geometry in asthma.

Methods: Twenty-six patients with steroid-naïve asthma, 30 patients with asthma treated with inhaled corticosteroids, and 46 age-matched healthy controls were studied. Serum periostin levels, lung function, and inflammatory cell counts in sputum were measured. The following parameters of airway dimension were assessed by computed tomography: lumen area, wall area (WA), WA to total area ratio, and wall thickness.

Results: Serum periostin levels were significantly elevated in patients with steroid-naïve asthma compared with the controls ($p < 0.01$) and patients with asthma who were treated with steroids ($p < 0.01$). In patients who were steroid naïve, serum periostin was correlated with air flow limitation ($r = -0.62$, $p < 0.01$) and the WA to body surface area ($r = 0.71$, $p < 0.01$), and sputum eosinophil percentage ($r = 0.60$, $p < 0.01$). Multivariate analysis showed that the percentage of predicted forced expiratory volume in 1 second, WA to body surface area, and sputum eosinophils were independent factors for high serum periostin.

Conclusion: Serum periostin may be a candidate for a novel biomarker for not only eosinophilic inflammation but as a marker for airway remodeling in asthma.

(Allergy Asthma Proc 37:225–230, 2016; doi: 10.2500/aap.2016.37.3945)

Asthma is characterized by airway inflammation and airway remodeling. T-helper type (Th) 2 cytokines such as interleukin (IL)-4, IL-5, and IL-13, and eosinophilic inflammation of the airway play a pivotal role in the pathogenesis of asthma.¹ Periostin is a 90-kDa matricellular protein that shares structural homology with fascilin I in insects.² Periostin can be induced by IL-4 and IL-13 stimulation in airway epithelial cells,^{3,4} and it has been localized in the bronchial subepithelial portion in asthma.⁵ Serum periostin concentrations are associated with persistent eosinophilic inflammation of the airways⁶ and with a greater decline in pulmonary function.⁷ Furthermore, periostin may contribute to airway remodeling in asthma because its expression in airway epithelial cells was correlated with basement membrane thickening.⁴ Therefore, the serum periostin level could be a useful marker for airway remodeling by reflecting airway Th2 cytokines and eosinophilic inflammation in asthma.

Airway wall thickening is a distinctive feature of remodeling, and high-resolution computed tomography (CT) has emerged as a reliable tool for noninvasive quantitative assessment magnitude and distribution of airway structural changes. When using CT to measure airway dimensions of segmental airways in asthma, wall thickness is increased in severe asthma compared with patients with mild asthma or normal control subjects.^{8–10} Inhaled corticosteroids (ICS) are widely recognized as a first-line therapy because they reduce the production of Th2 cytokines and they have a potent anti-inflammatory effect on the airway.¹¹ It is reported that airway wall thickness measured by CT is decreased after ICS treatment in steroid-naïve asthma.¹²

We hypothesized that, in patients with steroid-naïve asthma and who had symptoms and airflow limitation, an upregulated periostin may be associated with airway inflammation and airway remodeling. To test our hypothesis, serum periostin levels were compared in patients with steroid-naïve asthma, patients treated with ICS, and age-matched normal subjects, and the relationships among periostin and airway inflammation and airway wall geometry were examined.

METHODS

Subjects

Forty-six healthy control subjects and 56 patients with asthma, including 30 patients who received ICS

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The authors have no conflicts of interest to declare pertaining to this article
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(mean [standard deviation], 625 ± 234 $\mu\text{g/day}$ expressed as the equivalent dose of fluticasone propionate) and 26 patients who were steroid naive and treated with only short-acting β_2 -agonists as required were studied. Asthma was diagnosed according to the American Thoracic Society criteria,¹³ as a clear history of relevant symptoms and documented reversible airway obstruction ($>12\%$ improvement in forced expiratory volume in 1 second [FEV_1] after inhalation of a short-acting β_2 -agonist, and/or methacholine provocation concentration that causes a 20% fall in FEV_1 of <8 mg/mL). All the subjects were never smokers or were ex-smokers who had smoked for <5 pack-years but had stopped smoking >12 months before study enrollment. The patients had mild-to-moderate asthma with step 1 to 3 treatment of Global Initiative for Asthma,¹⁴ and healthy subjects with no history of allergic diseases served as controls. All the subjects gave their written informed consent, and the study protocol was approved by the International University of Health and Welfare Ethics Committee (13-A-12).

Serum Concentrations of Periostin and Immunoglobulin E Measurements

Periostin concentrations were measured by an enzyme-linked immunosorbent assay with the DuoSet Human Periostin/OSF-2 (R&D Systems, Minneapolis, MN). This enzyme-linked immunosorbent assay kit is specific for the measurement of natural and recombinant human periostin. It has been tested on human periostin isoforms 1 and 2, and cross-reacts with mouse periostin. Different samples that contained human periostin were diluted several fold (1:50 to 1:100). The mean (standard deviation) intra- and interassay coefficients of variability were $7.1 \pm 1.7\%$ and $7.6 \pm 1.9\%$, respectively. Total and allergen-specific serum immunoglobulin E (IgE) concentrations for house-dust, mites, cat dander, dog dander, cedar pollen, molds, and fungi were measured by using a radioallergosorbent test fluoroenzyme immunoassay (Phadia, Uppsala, Sweden). Specific IgE antibody levels of >0.7 UA/mL were considered positive results. Subjects who had at least one positive allergen-specific IgE antibody were regarded as atopic.

Pulmonary Function

Spirometry was performed by using computed spirometry (Fukuda Denshi, Tokyo, Japan). The predicted value of forced vital capacity and FEV_1 for a Japanese population were calculated by using the formula proposed by the Japanese Respiratory Society.¹⁵

CT Measurements

Scans were performed at full inspiration by using a 64-multislice scanner (Aquilion-64, Toshiba Medical,

Tokyo, Japan), as described previously.^{16,17} The CT scanning protocol was 120 kV, 200 mA, collimation of 0.5 mm, rotation time of 0.5 second, and pitch of 0.83. Images were reconstructed by using a bone algorithm at 1-mm slice thickness and an interval of 0.5 mm. The full-width at half-maximum principle¹⁸ was applied to determine the following airway parameters: luminal area (A_i), total area of the airway, wall area (WA) ($\text{WA} = \text{total area of the airway} - A_i$), absolute wall thickness (T), and percentage WA ($\text{WA}\%$) ($\text{WA}\% = \text{WA} / [\text{total area of the airway}] \times 100$) at the right upper lobe apical segmental bronchus. Because airway size may be affected by body size, airway WA was normalized to the body surface area (BSA).

Reproducibility of Airway Dimensions

All the airway dimensions were measured by one observer (J.O.) in a blinded fashion. Intraobserver error was tested by having this observer measure WA, T, and A_i in 10 randomly selected subjects twice at a 2-week interval. Interobserver error was determined by having two observers (J.O., K.A.) measure WA, T, and A_i in 10 randomly selected subjects. Analysis of intra- and interobserver reproducibility was conducted by using Bland-Altman analysis. For each plot, the mean difference did not appreciably deviate from zero, and the limits of agreement were small. Details about method reproducibility are described elsewhere.¹⁶

Sputum Induction

Sputum induction was performed by using a 5% hypertonic saline solution, and adequate plugs of sputum were separated from saliva as previously described.¹⁹ After treatment with 0.1% dithiothreitol and phosphate-buffered saline solution, slides were prepared by using cytospin and stained by using the May-Grünwald-Giemsa method. Differential cell counts were expressed as the percentage of 400 non-squamous cells.

Statistical Analysis

Data are presented as mean (standard deviation) or median (interquartile range). To compare each group, data were analyzed by analysis of variance with Bonferroni correction. Correlation analysis was performed by using the Pearson correlation coefficient. To assess the relative strength of association of periostin with possible contributing factors, we used a stepwise multiple regression analysis. A p value of <0.05 was considered significant. All data were analyzed with Stat-View software (SAS Institute, Cary, NC).

RESULTS

Characteristics of the Subjects

Baseline characteristics of the subjects are shown in Table 1. There were no significant differences among

Table 1 Subject characteristics

	Control (n = 46)	Steroid-Naive Asthma (n = 26)	Steroid-Treated Asthma (n = 30)
Age, mean (SD), y	48 ± 11	54 ± 13	57 ± 11
No. men/women	20/26	10/16	13/17
Body mass index, mean (SD), kg/m ²	24.7 ± 6.1	23.8 ± 3.6	24.1 ± 3.3
Asthma duration, mean (SD), y		19 ± 16	13 ± 11
Allergic dermatitis, no.		4	5
Allergic rhinitis, no.		15	16
Atopy, no.		23	21
Serum IgE, mean (SD), IU/mL		672.9 ± 754.3	533.0 ± 854.0
Serum periostin, median (IQR), ng/mL	22.4 (16.2–31.0)	37.6 (31.2–45.1)*#	26.2 (21.6–31.4)
Pulmonary function, mean (SD)			
FVC % predicted	108.0 ± 17.8	103.1 ± 16.9	106.7 ± 16.0
FEV ₁ % predicted	106.6 ± 16.1	85.2 ± 23.0§¶	91.5 ± 18.7
FEV ₁ /FVC, %	82.7 ± 5.9	68.6 ± 10.7§	70.2 ± 10.4
CT measurement, median (IQR)			
WA/BSA, mm ² /m ²	13.8 (11.0–15.7)	15.4 (14.2–18.8)*¶	14.9 (13.0–18.5)**
T/√BSA, mm/m	0.77 (0.69–0.87)	1.15 (0.92–1.21)§¶	1.02 (0.86–1.08)
WA, %	61.8 (58.4–65.4)	68.1 (64.5–70.6)§	67.3 (61.6–71.3)
Ai/BSA, mm ² /m ²	8.3 (5.8–10.6)	7.8 (6.1–10.0)	8.0 (5.8–9.4)
Sputum, median (IQR)			
Eosinophils, %	0.0 (0.0–5.0)	16.4 (7.6–44.4)#§	6.0 (0.9–27.0)**
Neutrophils, %	22.4 (11.1–40.8)	30.8 (16.5–54.0)	25.3 (5.8–45.1)

SD = standard deviation; IgE = immunoglobulin E; IQR = interquartile range; FVC = forced vital capacity; FEV₁ = forced expiratory volume in 1 second; CT = computed tomography; WA = airway wall area; BSA = body surface area; T = absolute wall thickness; Ai = luminal area.

**p* < 0.01, control vs steroid-naïve asthma.

#*p* < 0.01, steroid-naïve asthma vs steroid-treated asthma.

§*p* < 0.001, control vs steroid-naïve asthma.

¶*p* < 0.05, steroid-naïve asthma vs steroid-treated asthma.

||*p* < 0.001, control vs steroid-treated asthma.

***p* < 0.01, control vs steroid-treated asthma.

the three groups in age, sex distributions, and body mass index. Disease duration, the prevalence of allergic dermatitis or allergic rhinitis, and serum IgE levels did not differ between patients with steroid-naïve asthma and patients who were treated with steroids.

Serum Periostin Concentration

Serum periostin concentrations were significantly higher in patients with steroid-naïve asthma than in patients who were treated with steroids (*p* < 0.01) and control subjects (*p* < 0.01) (Table 1).

Pulmonary Function Tests

The percentage of predicted FEV₁ (FEV₁ %predicted) and FEV₁ to forced vital capacity were significantly lower in patients with asthma than in the healthy control subjects. Furthermore, FEV₁ %predicted was significantly lower in patients with ste-

roid-naïve asthma than in patients treated with steroids (*p* < 0.05) (Table 1).

Airway Dimensions

For indices of airway wall thickness, patients with asthma had significantly higher values of WA/BSA, T/√BSA, WA% than the control subjects. Both WA/BSA and T/√BSA were significantly increased in patients with steroid-naïve asthma compared with patients treated with steroids (*p* < 0.05, respectively) (Table 1). There was no significant difference in Ai/BSA among the three groups.

Induced Sputum

Sputum samples were obtained from 19 patients with steroid-naïve asthma, 24 patients treated with steroids, and 28 control subjects. The median (interquartile range) percentage of eosinophils in induced

Table 2 Relationships between serum periostin and clinical indices in asthma

Variables	Steroid-Naive Asthma		Steroid-Treated Asthma	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
FEV ₁ % predicted	−0.62	<0.01	−0.28	0.937
FEV ₁ /FVC, %	−0.54	<0.05	−0.19	0.846
WA/BSA, mm ² /m ²	0.71	<0.01	0.33	0.407
T/√BSA, mm/m	0.73	<0.01	0.21	0.875
WA, %	0.47	<0.05	0.17	0.171
Sputum eosinophils, %	0.60	<0.01	0.13	0.300

FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; WA = airway wall area; BSA = body surface area; T = absolute wall thickness.

sputum was significantly higher in patients who were steroid naive (16.4% [7.6–44.4%]) than in patients treated with steroids (6.0% [0.9–27.0%], $p < 0.01$) and control subjects (0.0% [0.0–5.0%], $p < 0.001$). There was no difference in sputum neutrophil percentage among the three groups (Table 1).

Association with Periostin and Clinical Variables

The relationships between serum periostin and spirometry, airway dimensions, and sputum eosinophils are shown in Table 2. Serum periostin levels were inversely correlated with FEV₁ %predicted ($r = -0.62$, $p < 0.01$) (Fig. 1 A) and positively correlated with WA/BSA ($r = 0.71$, $p < 0.01$) (Fig. 1 B) and percentage of sputum eosinophils ($r = 0.60$, $p < 0.01$) (Fig. 1 C) in patients with steroid-naive asthma. No significant correlations were observed between periostin levels and clinical variables in the patients treated with steroids or in the control subjects. In addition, pulmonary function data, *e.g.*, FEV₁ %predicted had significant correlations with WA/BSA and T/√BSA in patients with steroid-naive asthma (data not shown). The results of a multiple stepwise regression analysis that investigated the relationship between serum periostin with FEV₁ %predicted, WA/BSA, and sputum eosinophil percentage in patients with steroid-naive asthma are shown in Table 3. FEV₁ %predicted value, WA/BSA, and sputum eosinophils were independently associated with serum periostin after adjusting for age, sex, and body mass index.

DISCUSSION

In this study, we showed that serum periostin levels in patients with steroid-naive asthma was higher than in patients treated with steroids and in healthy subjects. In addition, serum periostin levels were inversely correlated with airflow limitation and positively correlated with airway wall thickness and sputum eosinophils in steroid-naive asthma. Moreover, multivariate regression analysis showed that FEV₁ %predicted,

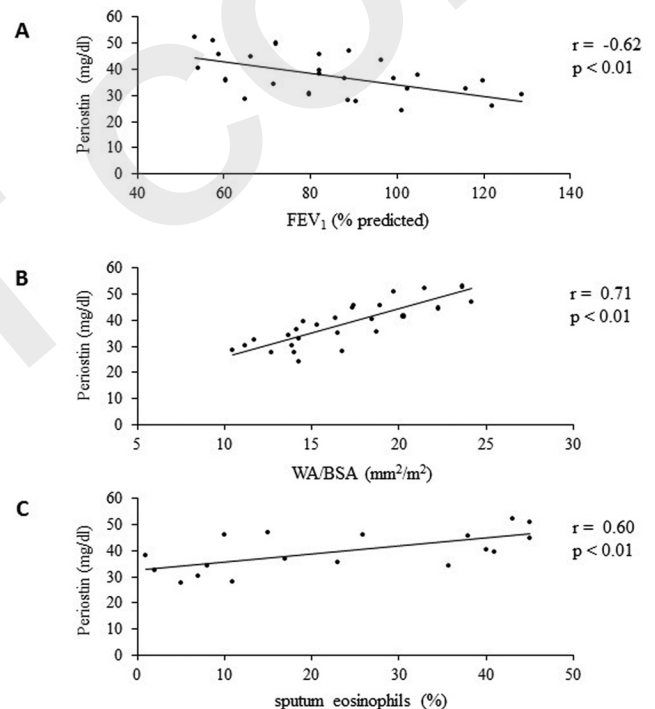


Figure 1. The correlation between serum periostin levels and (A) forced expiratory volume in 1 second (FEV₁), (B) wall area to body surface area (WA/BSA), and (C) sputum eosinophils in steroid-naive asthma.

WA/BSA, and sputum eosinophils were independent factors for high serum periostin. These results indicated that serum periostin not only could be a reliable biomarker for eosinophilic inflammation but also may contribute to the development of airway remodeling.

According to previous reports, serum periostin was associated with the blood eosinophil count and the number of eosinophils in tissue and sputum.^{6,7} The present data are in line with these findings that investigated the relationship between induced sputum eosinophilia and serum periostin levels. Wagener *et al.*²⁰ reported that there was a significant correlation between sputum eosinophil percentage and serum

Table 3 Multivariate stepwise analysis of steroid-naïve asthma with serum periostin as the dependent variable

Variables	Multivariate Analysis		
	β	95% CI	<i>p</i>
FEV ₁ , % predicted	−0.004	−0.014 to 0.006	0.03
WA/BSA, mm ² /m ²	0.003	−0.020 to 0.033	0.05
Sputum eosinophils, %	0.005	−0.011 to 0.019	0.04

CI = confidence interval; FEV₁ = forced expiratory volume in 1 second; WA = airway wall area; BSA = body surface area.

periostin levels when using the Elecsys Periostin assay (Roche Diagnostic, Penzberg, Germany) but not with the R&D assay. Two possible explanations for the discrepancy of our results are the clinical features of the cohorts and the periostin assay. The populations in the present study were patients who were steroid naïve, in contrast those described were steroid-treated patients in a previous study.²⁰ Furthermore, reproducibility of periostin in a previous study had the intra- and inter-assay coefficients of variability of 12.3% and 17.4%, respectively. In our assay results, the coefficients of variability were 7.1% and 7.6%, respectively. Because periostin can exist in multiple differentially spliced isoforms,²¹ the potential for confounding results due to different mixtures of isoforms in a biologic sample must be accounted for.²² In contrast to our study, serum periostin levels have been shown to be increased in patients who were taking a higher dose of ICS.⁷ The discrepancy in these results may be related to differences in patient selection and the severity of asthma, and it is possible that the expression of periostin in tissue was decreased by corticosteroids, which might be reflected in our findings. Recently, we demonstrated that inhaled steroid therapy reduced serum periostin and was associated with decreased wall thickness and decreased sputum eosinophils.²³ Blood eosinophil counts, sputum eosinophils, and fractional exhaled nitric oxide may reflect relatively acute eosinophilic inflammation, although serum periostin may be distinct from other biomarkers by integrating the information for chronic inflammation and remodeling.

Airway structural changes, such as subepithelial fibrosis, increased smooth-muscle mass, and goblet-cell hyperplasia contribute to airway remodeling. Although the components of the airway wall, including the subepithelium, mucosa, and smooth-muscle layers cannot be individually assessed by CT, we evaluated airway geometry of segmental bronchus as overall airway wall thickness and lumen area. In agreement with

previous studies, the luminal area in patients with asthma was similar to that in the controls.^{9,24} Subepithelial fibrotic change is considered a consequence of long-standing and persistent eosinophilic airway inflammation.^{25,26} The CT indices of airway dimensions reflect the pathologic changes in the airway wall (e.g., basement membrane thickness) in asthma.^{10,24}

In support of previous findings,^{8–10,16} the measurements of airway wall thickness were found to correlate with airflow limitation in steroid-naïve asthma. Recently, it was shown that patients with asthma and with high serum periostin concentrations were associated with a greater annual decline in lung function.⁷ The present findings also showed a progressive increase in airway wall thickness related to serum periostin levels. According to cluster analysis, late-onset eosinophilic asthma with higher serum periostin levels showed a rapid FEV₁ decline, even those who were well controlled using treatment with ICS.²⁷ Subepithelial fibrosis or airway remodeling is one factor that causes steroid resistance in asthma. These results indicated that airway remodeling in some populations may be hyporesponsiveness to ICS and usefulness of measuring serum periostin to predict tissue remodeling.

Periostin has been located to deposits of subepithelial fibrosis together with collagen, fibronectin, and tenascin in the asthma airway.⁵ Th2 cytokines, IL-4 and IL-13, share a common receptor chain (IL-4R α), which activates the signal transduction pathway and has a crucial role in subepithelial fibrosis.^{28–31} Another study reported that patients with a high serum periostin concentration had greater improvement in lung function with the IL-13 monoclonal antibody, lebrikizumab, than those who have uncontrolled disease despite ICS therapy.³² The value of a raised serum periostin concentration could potentially be used as a good predictor for targeting Th2 inflammation.

There were several limitations in the present study. First, only the right upper lobe apical segmental bronchus was assessed. Airway geometry of the subjects with asthma, and even if normal subjects, were found to narrow heterogeneously.³³ However, recent studies indicate that the dimensions of right upper lobe apical segmental bronchus were closely related to measurements of other bronchi.^{16,24,34} Second, the sample sizes were small. The authors speculate that the limited numbers of participants could potentially affect the accuracy of statistics. A larger population study is needed to examine the findings of this study as well to investigate the utility of serum periostin as a biomarker to predict response to therapies.

CONCLUSION

We found that serum periostin levels were significantly elevated in patients with steroid-naïve asthma

and were correlated with sputum eosinophils and airway wall thickness. It seems reasonable that serum periostin may be a key molecule that links Th2-eosinophilic inflammation and remodeling.

ACKNOWLEDGMENTS

The authors thank the staff of the Department of Laboratory Medicine, Atami Hospital for their technical assistance.

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