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Association of serum periostin with aspirin-exacerbated respiratory disease

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ABSTRACT

Background: Recent studies recommend periostin as a systemic biomarker of eosinophilic airway inflammation to predict responses to novel treatments that targets eosinophilic T_H2-driven inflammation in asthmatic patients.

Objective: To investigate the clinical implications of serum periostin levels in patients with aspirin-exacerbated respiratory disease (AERD) based on its overlapping T_H2-mediated pathogenesis with the eosinophilic asthma.

Methods: Serum periostin levels were measured by human periostin enzyme-linked immunosorbent assay (ELISA) in serum samples from 277 adults with asthma. Serum periostin levels were compared between patients with AERD and aspirin tolerant asthma (ATA) with other asthma phenotypes, such as severe or nonsevere asthma and eosinophilic or noneosinophilic asthma. The association of serum periostin levels with clinical parameters (including disease severity and comorbid condition) was analyzed.

Results: Serum periostin levels were significantly higher in patients with AERD vs ATA, patients with severe asthma vs nonsevere asthma, and patients with eosinophilic asthma vs noneosinophilic asthma ($P=.005$, $P=.02$, and $P=.001$, respectively). Multivariate regression analysis revealed serum periostin levels as a significant parameter to predict AERD phenotype ($P=.006$) together with severe asthma phenotype ($P=.04$). In addition, serum periostin levels correlated with blood eosinophil counts (Spearman $\tilde{r} = 0.244$, $P<.001$) and sputum eosinophil counts (Spearman $\tilde{r} = 0.261$, $P < 0.001$). Higher serum periostin levels were noted in comorbid AERD patients with more severe chronic rhinosinusitis (Lund-Mackay stages 3 and 4) than those with less severe chronic rhinosinusitis (Lund-Mackay stages 1 and 2) ($P = .03$).

Conclusion: Serum periostin levels are significantly elevated in AERD patients and associated with AERD phenotype and disease severity.

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Introduction

Asthma is a chronic airway inflammatory disorder with bronchial hyperresponsiveness that includes heterogeneous endotypes, such as allergic asthma, severe asthma, eosinophilic asthma, and aspirin-

exacerbated respiratory disease (AERD).^{1,2} Eosinophilic airway inflammation is a representative feature of asthma, and several biomarkers (such as sputum eosinophil, fractional exhaled nitric oxide, and serum periostin) have been developed.^{3,4} Efforts to identify different asthma phenotypes and/or endotypes have been made, and AERD represents an endotype related to phenotypes, such as eosinophilic asthma, exacerbation-prone asthma, and adult-onset asthma.¹

AERD is a chronic airway inflammatory condition that causes acute dyspnea and/or nasal symptoms after the ingestion of aspirin or other nonsteroidal antiinflammatory drugs (NSAIDs). Typical clinical features of the acetylsalicylic acid (aspirin or ASA) triad include chronic rhinosinusitis (CRS) complicated by nasal polyp

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(NP) formation, moderate to severe asthma, and hypersensitivity reactions to aspirin or other cross-reacting NSAIDs. The presence of eosinophilic inflammation in the upper and lower airway mucosa is the most remarkable AERD feature.^{5–10} AERD patients are more likely to present with severe asthma, poor lung function, higher requirements of systemic steroid burst, and life-threatening exacerbations.¹¹ The criterion standard to diagnose AERD is an aspirin challenge: routes of provocation include oral, bronchial inhalation, nasal inhalation, and intravenous challenge.⁶ However, patients should have a baseline forced expiratory volume in 1 second (FEV₁) of at least 70% of the predicted value to avoid serious complications. There is no routinely proposed in vitro test to confirm aspirin hypersensitivity. However, some experimental tests (measurement of cysteinyl leukotriene release, basophil activation test, measurement of aspirin-triggered 15-hydroxyeicosatetraenoic acid release from peripheral blood lymphocytes, and eosinophil-derived neurotoxin) have been suggested.^{5,12} Therefore, noninvasive methods for the diagnosis of AERD need to include a serologic biomarker for clinical practices as an alternative test to an aspirin challenge test in AERD patients and to determine asthma endotypes.

Periostin is a secreted 90-kDa extracellular matrix protein that is structurally homologous with the insect cell adhesion molecule fasciclin I and can be induced by interleukin (IL) 4 and IL-13.^{13–15} Periostin has been recently studied in various medical fields, such as allergy, asthma, interstitial lung disease, myocardial infarction, cancer, cancer stem cells, osteoporosis, wound healing, periodontal diseases, and peritoneal fibrosis, because of its contribution to tissue development and remodeling.¹⁶ In 2011, the results of a randomized, double-blind, placebo-controlled study of lebrikizumab (a monoclonal antibody to IL-13) treatment was reported, and serum periostin was highlighted because of a greater lung function improvement for patients with high pretreatment serum periostin levels.¹⁷ Another study reported periostin as the single best predictor of eosinophilic airway inflammation compared with other biomarkers, such as IgE levels, blood eosinophil count, and fractional exhaled nitric oxide levels.³ On the basis of these findings, periostin is thought of as a marker of T_H2-mediated eosinophilic inflammations.^{16,18} In addition, periostin may contribute to airway remodeling in asthmatic patients because of its increased expression in airway epithelium and deposition in the airway subepithelial layer.^{14,19} Kanemitsu et al²⁰ reported serum periostin as a useful biomarker for the development of airflow limitation in asthmatic patients treated with an inhaled corticosteroid (ICS). Evidence of the overlapping mechanism of asthma and AERD has been reported in relation to T_H2 and eosinophilic inflammation; consequently, we investigated the clinical implication of the serum periostin levels in the AERD phenotype.

Methods

Study Design

A retrospective cross-sectional study was conducted to evaluate the differences of serum periostin level in asthmatic adults according to the phenotypes, including AERD, and clinical parameters.

Patients

We measured serum periostin levels in 277 asthmatic adults (89 men and 188 women, 18 to 75 years old) registered in the Ajou Asthma Registry who visited the department of Allergy and Clinical Immunology, Ajou University Hospital. Asthma was diagnosed according to the Global Initiative for Asthma guideline by clinicians (allergy specialists).² Patients with acute asthma exacerbation were excluded but enrolled at stable state to minimize the enrollment of patients using systemic steroids. We enrolled 87 healthy volunteers without any allergic disease histories as controls. Mean (SD) age of

healthy controls was 27.3 (6.3) years (range, 22–57 years), 56.3% of study participants were men.

Serum samples were obtained and frozen at –70°C after collection and thawed immediately before use. Patient clinical data were obtained from the Ajou Asthma Registry database and from electronic medical records reviewed by the clinicians. The protocols used in this study were reviewed and approved by the Ajou University Institute Review Board. Written informed consent was obtained from each patient.

Collection of Clinical Data

The analysis included age, sex, atopy, smoking status (current, former, or never smoker), blood eosinophil count, total IgE, eosinophilic cationic protein (ECP), sputum eosinophil count, FEV₁ (percentage predicted), provocation concentration that caused a decrease in FEV₁ of 20% on methacholine challenge test, percentage decrease of FEV₁ on lysine-aspirin bronchoprovocation test (Lys-ASA BPT), and comorbid condition of CRS and/or NP, and Lund-Mackay (LM) scores. Atopy was defined by a positive skin prick test result to a common inhalant allergen (tree mixture, grass mixture, mugwort, ragweed, cat fur, dog fur, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and *Alternaria* [Bencard, Bretford, United Kingdom]), in which a positive reaction was defined as the ratio of the mean wheal diameter of the allergen to histamine of 1 or higher. Total IgE and ECP levels were measured with the ImmunoCAP (ThermoFisher Scientific, Uppsala, Sweden) system. The comorbid condition of CRS and/or NP of patients was defined by symptoms and rhinoscopy results, paranasal sinus radiography, and/or sinus computed tomography (CT). The LM scores (counted by LM staging system for CRS in sinus CT) were graded into 4 stages (stage 1, scores of 0–4; stage 2, scores of 5–9; stage 3, scores of 10–14; and stage 4, scores of 15–24).²¹

Determination of Asthma Phenotype

The assessment of asthma phenotypes that included AERD and ATA, severe and nonsevere asthma, and eosinophilic and non-eosinophilic asthma was performed in each asthma patient by clinicians. AERD was defined by a typical clinical history (development of upper or lower respiratory tract symptoms after the ingestion of

Table 1
Patient characteristics

Characteristic	Value (N = 277)
Male/female, No.	89/188
Age at enrollment, mean (SD), y	46.4 (12.8)
Atopy/nonatopy, No.	137/139
Smoker/nonsmoker, No.	53/79
Blood eosinophil count, mean (SD), /μL	415.0 (420.3)
Total IgE, mean (SD), IU/L	363.6 (658.0)
ECP, mean (SD), μg/L	41.2 (40.5)
Serum periostin, mean (SD), ng/mL	76.5 (35.2)
Sputum eosinophil count, mean (SD), % (n = 187) ^a	26.2 (35.8)
FEV ₁ at enrollment, mean (SD), % predicted	87.4 (20.7)
PC ₂₀ at methacholine challenge test, median (range) (n = 122) ^a	1.5 (0.1–23.7)
Percentage decrease of FEV ₁ after Lys-ASA BPT (n = 126) ^a in AERD, mean (SD)	23.1 (10.4)
CRS with NPs/CRS without NP, No.	41/83
Lund-Mackay stage (1/2/3/4, n = 130) ^a	29/31/24/46
AERD/ATA, No.	149/128
Severe/nonsevere asthma, No.	56/221
Eosinophilic/non-eosinophilic asthma, No.	93/94

Abbreviations: AERD, aspirin-exacerbated respiratory disease; ATA, aspirin tolerant asthma; CRS, chronic rhinosinusitis; ECP, eosinophilic cationic protein; FEV₁, forced expiratory volume in 1 second; Lys-ASA BPT, lysine-aspirin bronchoprovocation test; PC₂₀, provocation concentration that caused a decrease in FEV₁ of 20%; NP, nasal polyp.

^aThe number of totally investigated patients is given if clinical parameters were not investigated in all patients.

aspirin or other NSAIDs) and/or positive results to Lys-ASA BPT⁵; however, negative responders to Lys-ASA BPT or patients who denied any changes of upper and lower respiratory tract symptoms after aspirin or NSAID exposure were defined as having ATA. Lys-ASA BPT was performed with increased doses of Lys-ASA solution up to 300 mg/mL using methods previously described and with peripheral blood collection at the end of the examination if patients agreed.²² The Lys-ASA BPT result was identified as positive when the FEV₁ decreased 15% or more after the challenge.⁵ A total of 149 patients had AERD and 128 patients had ATA. Serum periostin levels were compared before and after the Lys-ASA BPT in 89 patients.

Severe asthma was diagnosed according to a definition developed at an American Thoracic Society workshop on refractory asthma. Signs of ongoing poor asthma control (daily symptoms, additional medical use, high health care use, and abnormal lung function) despite treatment with a high dose of corticosteroids (at least 1,000 µg of fluticasone dipropionate or equivalent per a day) identified severe asthma.^{23,24} Eosinophilic asthma was defined as 3% or more eosinophils in induced sputum.³

Measurement of Serum Periostin Level

Periostin levels were measured with a proprietary sandwich ELISA (Shino-test, Kanagawa, Japan), as described previously (see Measurements of Serum Periostin).¹⁶ Briefly, a human periostin ELISA was conducted using 2 rat antihuman periostin monoclonal antibodies (clones SS18A and SS17B). SS18A was incubated overnight at 25°C, and then diluted serum samples (1/200) were incubated overnight at 25°C after blocking with 0.5% casein in Tris-buffered saline. Peroxidase-labeled SS17B (50 ng/mL) was added and incubated for 1.5 hours at 25°C. The different absorbances at 450 and 550 nm were evaluated after an addition of reaction solution. ELISA was performed on duplicated samples.

Statistical Analysis

Statistical analyses were performed with SPSS statistical software, version 19 (SPSS Inc, Chicago, Illinois). Spearman rank correlation analysis identified associations among continuous clinical parameters. The Mann-Whitney test and χ^2 test compared the unpaired continuous and dichotomous variables, and the Wilcoxon

signed rank test compared the paired continuous variables. A receiver operating characteristic (ROC) curve analysis discriminated asthmatic patients from healthy controls. Logistic regression analyses defined the associations of continuous and dichotomous variables to AERD phenotype.

Results

Patient Characteristics

Table 1 gives the clinical data of the study patients. Serum periostin levels in the asthmatic patient group were significantly higher than levels found in healthy controls (mean [SD], 76.5 [35.2] ng/mL, 46.2 [29.0] ng/mL; $P < .001$). An ROC curve analysis showed significant differences of serum periostin levels between asthmatic patients and healthy controls (area under curve = 0.75, $P < .001$), and the cutoff value of the serum periostin level that discriminated asthmatic patients from healthy controls was 54.5 ng/mL, with 71.8% sensitivity and 63.2% specificity.

Association of Serum Periostin Levels with Clinical Parameters in Asthma

Serum periostin levels were not correlated with age (Spearman $\rho = -0.006$, $P = .92$); however, a significant difference was observed between men and women ($P = .01$). No significant differences in serum periostin levels were found according to atopic status ($P = .92$) and smoking history ($P = .27$). Serum periostin levels were positively correlated with blood eosinophil (Spearman $\rho = 0.244$, $P < .001$, Fig 1A) and sputum eosinophil count (Spearman $\rho = 0.261$, $P < .001$, Fig 1B); however, serum periostin levels were not significantly correlated with serum total IgE or ECP levels (Spearman $\rho = 0.087$, $P = .15$; Spearman $\rho = 0.061$, $P = .39$, respectively).

Comparison of Serum Periostin Levels According to Asthma Phenotypes

Significantly higher serum periostin levels were noted in AERD patients compared with ATA patients ($P = .005$, Fig 2A) and in patients with severe asthma compared with nonsevere asthma ($P = .02$, Fig 2B). Serum periostin levels in patients with eosinophilic asthma were significantly higher than levels found in patients with noneosinophilic asthma ($P = 0.001$, Fig 2C). In addition, serum

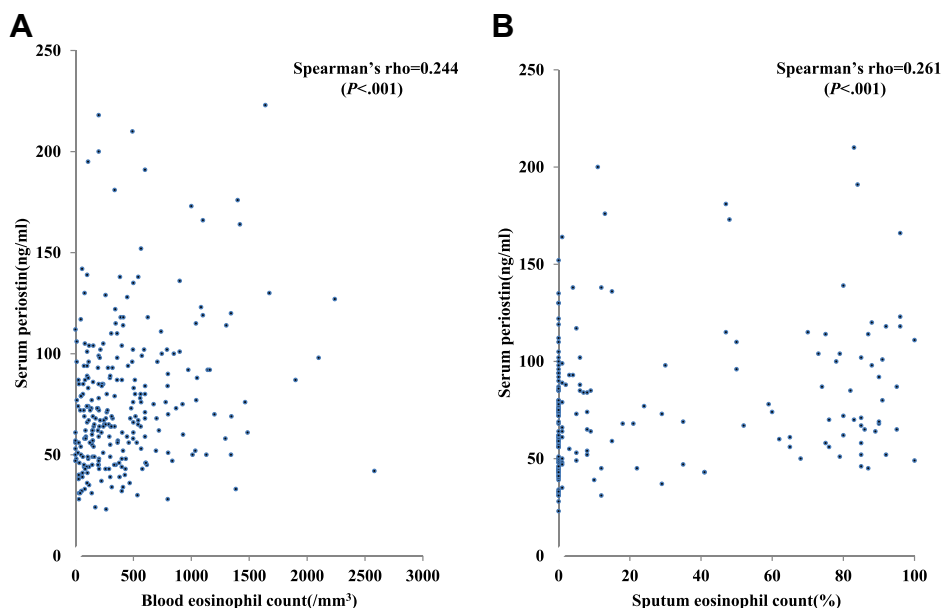


Figure 1. Correlations of serum periostin levels with blood eosinophil counts (A) and sputum eosinophil counts (B). Serum periostin levels were positively correlated with blood eosinophil counts (Spearman $\rho = 0.244$, $P < .001$; A) and sputum eosinophil count (Spearman $\rho = 0.261$, $P < .001$; B).

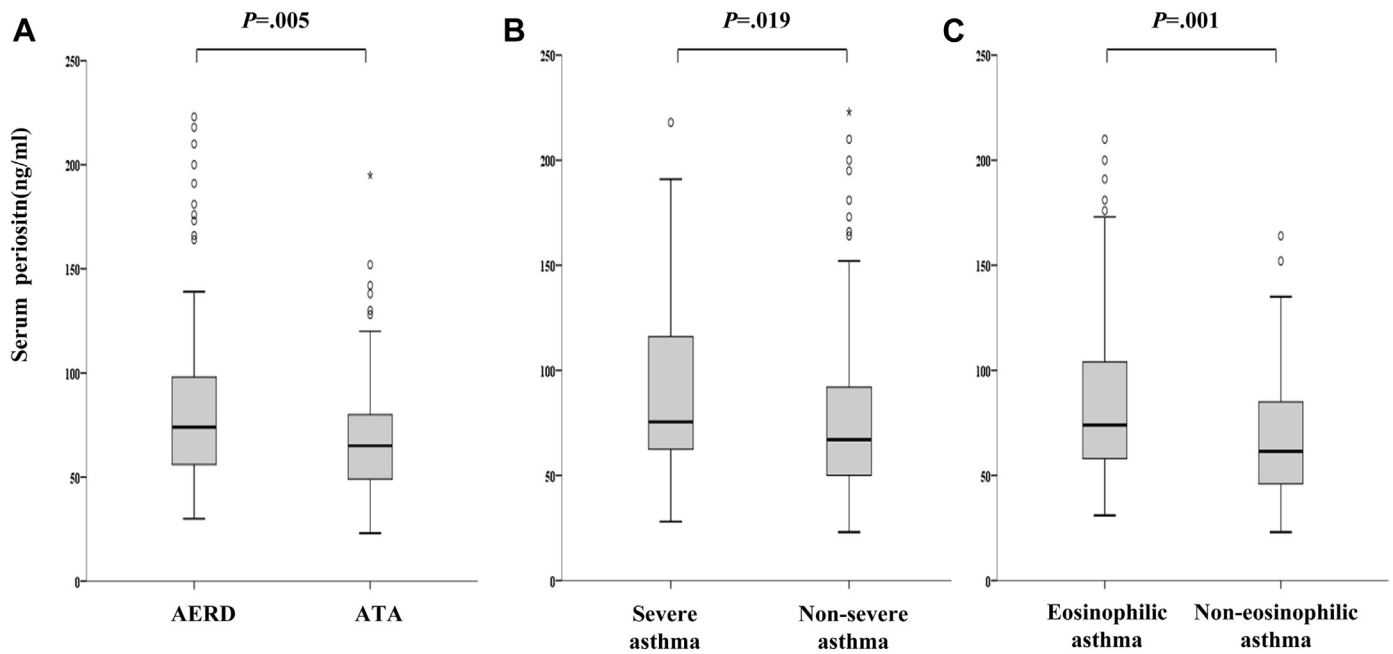


Figure 2. Comparisons of serum periostin level according to asthma phenotypes: A, aspirin-exacerbated respiratory disease (AERD) and aspirin tolerant asthma (ATA); B, severe and nonsevere asthma; and C, eosinophilic and noneosinophilic asthma. Serum periostin levels were significantly higher in patients with AERD ($P = .005$, A), patients with severe asthma ($P = .02$, B), and patients with eosinophilic asthma ($P = .001$, C).

periostin levels were significantly higher in asthmatic patients with CRS than those without CRS ($P < .001$). Furthermore, asthmatic patient with CRS and NPs had significantly higher serum periostin levels compared with those with CRS without NPs ($P = .002$).

The ROC curve analysis that discriminated AERD from ATA in total asthma patients indicated that the cutoff value of the serum periostin level (that discriminated the AERD phenotype) was 81.5 ng/mL, with 44.3% sensitivity and 75.8% specificity ($AUC = 0.597$, $P = .005$). The ROC curve between severe asthma and nonsevere asthma revealed that the cutoff value of the serum periostin level (that discriminated the severe asthma phenotype) was 64.5 ng/mL, with 75.0% sensitivity and 47.1% specificity ($AUC = 0.602$, $P = .02$).

Association of Serum Periostin Level with AERD Phenotype

Table 2 summarizes the predictability of each clinical parameter for AERD using univariate and multivariate regression analysis. Serum periostin and severe asthma phenotype were the significant

parameters associated with AERD phenotype ($P = .003$ and $P = .02$, respectively) in the univariate analysis, and serum periostin remained a significant parameter after adjusting for other parameters associated with periostin levels, such as sex, severe asthma phenotype, and eosinophilic asthma phenotype ($P = .006$). Severe asthma was also remained significant after adjusting other parameters ($P = .04$).

Association of Serum Periostin Levels with Disease Severity of AERD

Within the AERD group, AERD patients with more severe CRS (LM stages 3 and 4) had significantly higher serum periostin levels than patients with less severe CRS (LM stages 1 and 2) ($P = .03$). AERD patients with severe asthma did not have a significant difference of serum periostin level compared with AERD patients without severe asthma ($P = .09$). A significantly higher serum periostin level was found in AERD patients with eosinophilic asthma vs those without eosinophilic asthma ($P = .005$). Significant

Table 2
Predictability for the AERD phenotype by univariate and multivariate logistic regression analyses

Variable	Univariate		Multivariate	
	OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age	0.988 (0.970–1.007)	.22		
Sex (male)	1.153 (0.694–1.914)	.58	1.476 (0.771–2.824)	.24
Atopy	1.382 (0.860–2.221)	.18		
Severe asthma	2.092 (1.126–3.888)	.02	2.171 (1.049–4.490)	.04
Eosinophilic asthma	1.068 (0.601–1.897)	.82	0.754 (0.403–1.409)	.38
Blood eosinophil count, μ L	1.000 (0.999–1.000)	.56		
Total IgE, IU/L	1.000 (1.000–1.001)	.14		
ECP, μ g/L	1.001 (0.994–1.008)	.75		
Serum periostin, ng/mL	1.012 (1.004–1.019)	.003	1.014 (1.004–1.024)	.006
Sputum eosinophil count, %	1.005 (0.997–1.013)	.25		
Predicted FEV ₁ , %	1.002 (0.990–1.013)	.77		
CRS with NPs	1.892 (0.835–4.287)	.13		
LM stages 3 and 4	1.786 (0.861–3.704)	.12		

Abbreviations: AERD, aspirin-exacerbated respiratory disease; CI, confidential interval; CRS, chronic rhinosinusitis; ECP, eosinophilic cationic protein; FEV₁, forced expiratory volume in 1 second; LM, Lund-Mackay; OR, odds ratio.

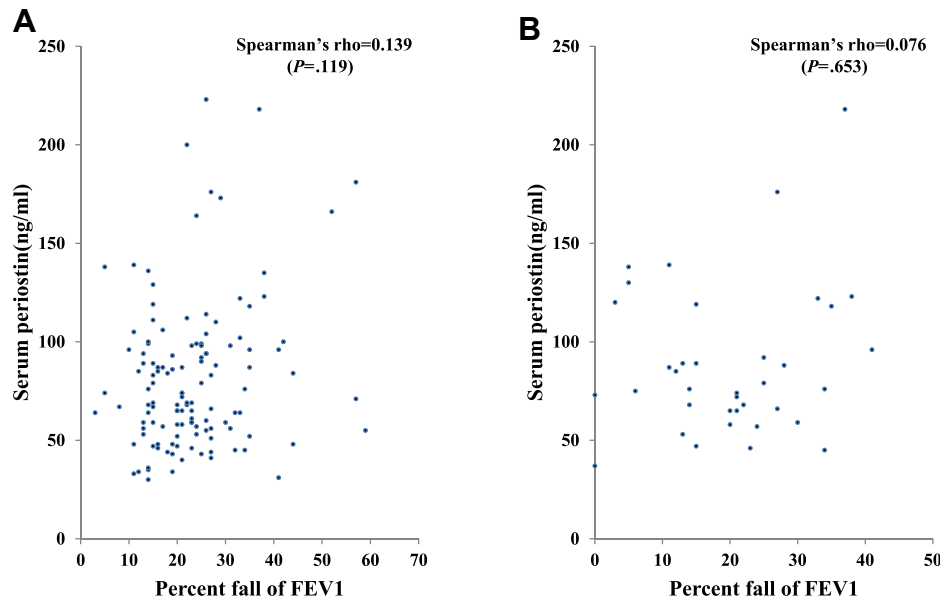


Figure 3. Correlation of serum periostin levels and percentage decrease in forced expiratory volume in 1 second (FEV_1) after lysine-aspirin bronchoprovocation test (Lys-ASA BPT) in patients with aspirin-exacerbated respiratory disease (AERD) (A) and severe asthma (B). A significant positive correlation was not noted between serum periostin level and the percentage decrease in FEV_1 after Lys-ASA BPT in AERD patients (Spearman $\rho = 0.139$, $P = .12$) and in severe asthma patients (Spearman $\rho = 0.076$, $P = .65$).

positive correlations were noted between serum periostin levels and blood eosinophil count (Spearman $\rho = 0.217$, $P = .008$, $n = 148$) and sputum eosinophil count (Spearman $\rho = .282$, $P = .005$, $n = 99$), whereas the percentage decrease in FEV_1 after Lys-ASA BPT in AERD patients was not significantly correlated with serum periostin levels (Spearman $\rho = 0.139$, $P = .12$, $n = 126$, Fig 3A). In addition, no significant correlation was noted in patients with severe asthma between serum periostin levels and the percentage decrease of FEV_1 after Lys-ASA BPT (Spearman $\rho = 0.076$, $P = .65$, $n = 37$, Fig 3B).

Comparison of Serum Periostin Levels Before and After Lys-ASA BPT

Serum periostin levels (compared before and after Lys-ASA BPT in 89 asthmatic patients) indicated no significant changes after

Lys-ASA BPT in the AERD ($P = .20$, Fig 4A) and ATA groups ($P = .71$, Fig 4B). In addition, no significant changes were noted in accordance with sex ($P = .38$ for men with AERD, $P = .68$ for men with ATA, $P = .39$ for women with AERD, and $P = .90$ for women with ATA).

Discussion

This study found a significantly higher serum periostin level in asthmatic patients compared with healthy controls and a serum periostin level of 67.5 ng/mL as a cutoff value to discriminate asthmatic adults from healthy controls. This cutoff value might be considered a lower value than previously reported²⁰; the mean (SD) age of the participants in a previous report was 62.3 (13.7) years, and 76.3% were female, somewhat different from our asthma

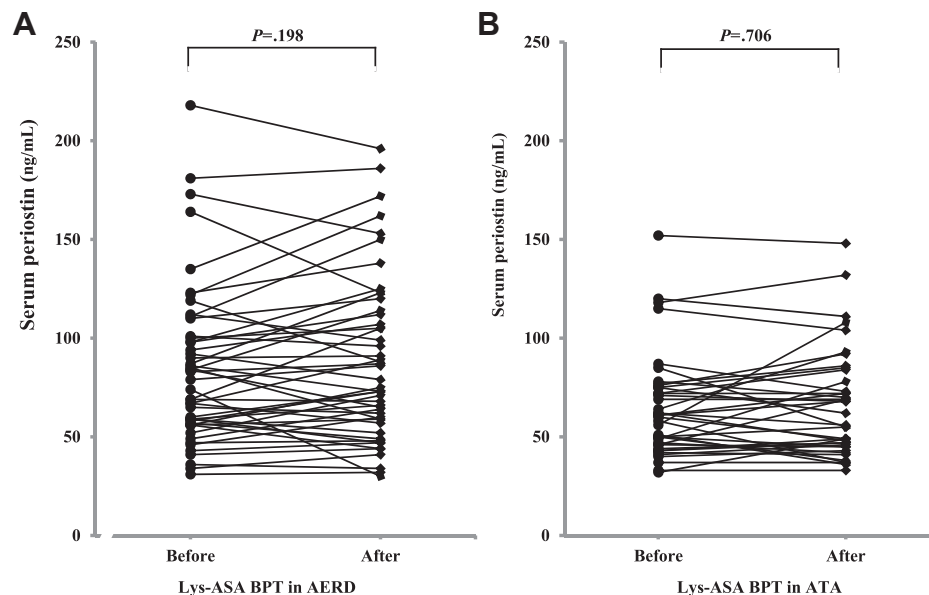


Figure 4. Comparisons of serum periostin levels before and after lysine-aspirin bronchoprovocation test (Lys-ASA BPT) in patients with aspirin-exacerbated disease (AERD) (A) and aspirin tolerant asthma (ATA) (B). No significant changes were found between before and after Lys-ASA challenges in the AERD and ATA groups ($P = .20$, A; $P = .71$, B).

population. The authors targeted a cutoff value of the highest specificity rather than sensitivity. Two consistent findings with previous reports are the significant correlation of the serum periostin level with the blood eosinophil and sputum eosinophil counts along with significantly higher periostin levels in patients with severe asthma and eosinophilic asthma.^{3,20} The novel finding in the present study was that serum periostin revealed a significant association with the AERD phenotype: (1) a significantly higher serum periostin level in AERD than in ATA and (2) predictability for AERD after adjusting for associated asthma phenotypes, such as severe asthma and eosinophilic asthma. On the basis of these findings, we thought that there might be a significant association between serum periostin level and AERD phenotype.

In AERD, a more intense eosinophilic infiltration in upper and lower airway mucosa and up-regulation of eosinophil-related cytokines have been reported,^{5,25–28} which are closely associated with severe CRS and/or NPs,¹¹ and severe asthma.²⁰ In addition, there is increased evidence that periostin is a reliable biomarker for eosinophilic airway inflammation. Moreover, production of periostin is up-regulated in allergic rhinitis and CRS with NPs.^{29,30} Secretion of periostin from lung fibroblast could be stimulated by IL-4 and IL-13, and blood periostin was reported as the single best predictor of airway eosinophilia in adult asthmatic patients.^{3,14} Therefore, lebrikizumab (a novel T_H2 -targeted treatment) played a more efficient role in lung function improvement for asthmatic patients with higher serum periostin levels. Johansson et al.²⁵ found that eosinophils stimulated by IL-5 were guided to areas of high periostin density in an asthmatic airway by the adhesion of eosinophils $\alpha_M\beta_2$. In the present study, serum periostin levels were significantly higher in AERD patients with the eosinophilic type or more severe CRS when the serum periostin level was analyzed with clinical parameters within the AERD group, indicating that serum periostin level can be a reliable serum biomarker to predict the phenotype of AERD, especially those with the eosinophilic type or more severe CRS. A higher incidence of severe asthma, irreversible airway obstruction, and lower postbronchodilator FEV₁ are typical clinical features of AERD that contribute to more frequent health care use, intubation, steroid burst, and higher requirements for high-dose ICSs.^{11,20} These characteristics are believed to reflect airway remodeling characterized by subepithelial fibrosis, thickening of the lamina reticularis, and deposition of extracellular matrix proteins that might be due to fibrosis after an eosinophilic airway inflammation.^{31–35} Some investigators reported that periostin could be a candidate for a novel component that contributes to subepithelial fibrosis because it could be overexpressed in response to IL-4 and/or IL-13 (representative T_H2 cytokines) in lung fibroblast and bind to extracellular matrix proteins.^{14,36,37} An increased serum periostin level in asthmatic patients with greater airflow limitation is understood in the same context.²⁰ In the present study, serum periostin level tended to be higher in AERD patients with severe asthma. Consequently, we hypothesized that more severe T_H2 -driven inflammation (including eosinophilic infiltration found in AERD) could trigger an overexpression of the *POSTN* gene that could result in an increased serum periostin level and deposition of periostin in the upper and lower airway mucosa, which progresses to subepithelial fibrosis with more severe clinical characteristics of AERD.

The pathogenesis of AERD is explained by 2 mechanisms related to leukotriene overproduction.^{5,38,39} The first mechanism is in association with aspirin-induced acute respiratory reactions, and the second mechanism is the chronic eosinophilic inflammation of the upper and lower airway mucosa related to the chronicity of AERD. AERD patients present with severe upper and lower airway symptoms with a high prevalence of CRS and/or NPs.⁸ We believe that periostin may be involved in AERD pathogenesis under the control of T_H2 cytokines (such as IL-4 and/or IL-13), especially in the

chronicity mechanism of AERD pathogenesis, because of the absence of significant changes in periostin levels during the Lys-ASA BPT.

In conclusion, we found that serum periostin is significantly elevated in AERD patients, especially those with more severe CRS, suggesting that serum periostin can be a potential biomarker for AERD beyond T_H2 -mediated or eosinophilic airway inflammations.

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