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Original article

Phenotype of asthma related with high serum periostin levels



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ABSTRACT

Background: Asthma is a heterogeneous disease composed of various phenotypes. Periostin, a molecule inducible with interleukin (IL)-4 or IL-13 in bronchial epithelial cells, is a biomarker of “TH2-high” asthma. The objective of this study is to examine whether the serum periostin concentrations are correlated with the severity, specific phenotype(s), or comorbidity of asthma.

Methods: Serum concentrations of periostin were measured in 190 Japanese asthmatic patients and 11 healthy controls. The protocol was registered under UMIN 000002980 in the clinical trial registry.

Results: The serum concentrations of periostin were significantly higher ($P = 0.014$) in asthmatics [70.0 (54.0–93.5) ng/ml] than in healthy subjects [57.0 (39.0–63.0) ng/ml], though we found no correlation between serum periostin concentrations and treatment steps required to control asthma. To characterize “high-periostin” phenotype(s), the patients with asthma were divided among tertiles based on the serum concentrations of periostin. The high-periostin group was older at onset of asthma ($P = 0.04$), had a higher prevalence of aspirin intolerance ($P = 0.04$) or concomitant nasal disorders ($P = 0.03–0.001$), higher peripheral eosinophil counts ($P < 0.001$), and lower pulmonary function ($P = 0.02–0.07$). The serum concentrations of periostin were particularly high in asthmatic patients complicated by chronic rhinosinusitis with nasal polyps and olfactory dysfunction. In contrast, neither atopic status, control status of asthma, nor quality of life were related with the “high-periostin” phenotype.

Conclusion: Elevated periostin concentrations in serum were correlated with a specific phenotype of eosinophilic asthma, late-onset and often complicated by obstructive pulmonary dysfunction and nasal disorders.

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Introduction

Asthma is an inflammatory disease of the airways characterized by bronchial hyperresponsiveness and reversible airflow limitation, affecting about 300 million people in the world.¹ While

airway inflammation and respiratory symptoms can be controlled with inhaled corticosteroids in most instances, they remain refractory to the highest tolerable doses of inhaled corticosteroids, long-acting bronchodilators, and leukotriene receptor antagonists in patients with severe asthma.² The frequent disease exacerbations suffered by these patients, and multiple emergency department visits and hospitalisations represent a heavy social and economic burden.³ Furthermore, because the heterogeneous characteristics of severe asthma preclude its control by a single therapeutic agent, relevant phenotyping and individualized treatment are essential.⁴

Interleukin (IL)-13, a TH2 cytokine, plays an important role in the development and persistence of eosinophilic inflammation and hyperresponsiveness in the asthmatic airways.⁵ Patients with “TH2-high” asthma have been identified by transcriptome analysis, whose bronchial epithelial cells express excessive amounts of IL-13-inducible genes, such as *Cla1* and *Postn*.⁶ These patients present with increased eosinophilic inflammation and airway hyperresponsiveness, thickened basement membranes, and greater responsiveness to corticosteroids.⁷ On the other hand, periostin, the product of IL-13-inducible *Postn*, is an extracellular matrix protein of the fasciclin family,⁸ and can be measured in serum. Serum periostin concentrations are correlated with a sustained eosinophilic inflammation of the airways⁹ and rapid decline of pulmonary function¹⁰ despite treatment with inhaled corticosteroids. Another study has suggested that the concentrations of serum periostin can be used to predict the responsiveness to treatment with anti-IL-13 antibody.¹¹ Therefore, periostin might be a useful biomarker as a companion diagnostic for severe asthma.¹² However, clinical characteristics or phenotype of asthmatics with elevated serum periostin levels are not well studied. This study examined whether, in asthmatic Japanese, the serum concentrations of periostin are correlated with the disease severity, specific phenotype or comorbidity.

Methods

Patient populations

Between April 1, 2010 and December 31, 2012, we enrolled Japanese patients ≥ 20 years of age, who presented with difficult-to-treat asthma at Keio University Hospital and affiliated hospitals. Asthma was diagnosed on the basis of the Japanese Society of Allergology guideline.¹³ Asthma requiring step 4 or 5 treatment actions, defined in the updated version of the 2006 statement by the Global Initiative for Asthma (GINA) to achieve its optimum control was defined as severe asthma.¹⁴ Healthy subjects with no history of allergic diseases and patients with mild to moderate asthma controlled with step 1 to 3 treatment actions of GINA, served as controls. Patients with uncontrolled malignant tumours or widespread lung disease that prominently impaired lung function were excluded from enrolment. The protocol (no 2009-9-5) initially approved by the Institutional Review Board of Keio University School of Medicine, was subsequently approved by the Review Board of each participating institution, and implemented in compliance with the Declaration of Helsinki. All participants granted their written informed consent.

Collection of clinical information

The study participants reported their clinical information at the time of enrolment by means of a self-completed questionnaire. Poor adherence to the treatment was defined as < 5 day-use of inhaled corticosteroids per week. Olfactory dysfunction was defined by the presence of hyposmia/anosmia. The control status of

asthma and the disease-specific quality of life were ascertained, using the Japanese versions of the asthma control test¹⁵ and the Juniper's asthma quality of life questionnaire,^{16,17} respectively. Laboratory data and information pertaining to medications and disease exacerbations were collected from medical records.

Serum concentrations of periostin and cytokines

The serum periostin concentrations were measured by enzyme-linked immunosorbent assay, as previously reported.¹⁸ The serum concentrations of IL-4, IL-5, and IL-13 were measured, using the Bio-Plex[®] Suspension Array System (Bio-Rad Laboratories, Hercules, CA, USA). Total and allergen-specific serum immunoglobulin (Ig)E concentrations for house-dust mites, cat dander, fungi, and insects were measured using a fluorescence-enzyme immunoassay (Mitsubishi Chemical Medience Corporation, Tokyo, Japan). Atopic asthma was defined as one or more allergen-specific IgE concentrations > 0.70 UA/mL.

Pulmonary function tests

Pulmonary function during stable asthma was measured using a CHESTAC-9800 spirometer (Chest, Tokyo, Japan), which met the criteria of the American Thoracic Society. The predicted value of vital capacity (VC) and forced expiratory volume in 1 s (FEV₁) for a Japanese population was calculated using the formula proposed by the Japanese Respiratory Society. The fraction of exhaled nitric oxide was measured with a Sievers nitric oxide analyser (GE Healthcare Japan, Tokyo, Japan) in some participating institutions.

High-resolution computed tomography

Airway wall thickness was measured by high-resolution computed tomography scans, using an AquilionTM (TOSHIBA Medical Systems Corporation, Tochigi, Japan) or LightSpeed[®] volume scanner (GE Healthcare). The wall area and % wall area of the apical bronchus of the right upper lobe (RB1) were measured using the AZE VirtualPlace Lexus64[®] software (AZE, Tokyo, Japan).

Statistical analysis

The data are expressed as means \pm SD, median and interquartile range, or percentages. Categorical data were analysed with the chi-square test. Mann–Whitney test or Kruskal–Wallis test, as appropriate. Spearman's rank correlation coefficient was determined between serum levels of periostin, TH2 cytokines, and blood eosinophil counts. A regression analysis was performed to examine the correlations between pulmonary functions and age- and sex-adjusted or unadjusted, log-transformed serum periostin concentration, duration of asthma and smoking history. A statistically significant difference was defined as a two-tailed *P* value < 0.05 . All statistical analyses were performed with the SPSS statistical software package for Windows, version 20.0 (IBM Corporation, Armonk, NY, USA).

Results

Characteristics of the study groups

This study enrolled 11 healthy subjects (mean age 39.5 ± 12.1 years, 73% men) and 190 asthmatic patients (mean age 60.2 ± 14.5 years, 44% men), including 22 in the GINA steps 1 and 2, 20 in step 3, 83 in step 4 and 65 patients in step 5. In 58 patients in step 4 (70%) and 58 patients in step 5 (89%), the status corresponded to the definition of severe asthma by international ERS/ATS

Table 1
Characteristics of the study groups.

	GINA steps		P
	1–3 (n = 42)	4 & 5 (n = 148)	
Demographic and clinical observations			
Men	38	46	0.39
Age, y	60.6 ± 14.3	60.1 ± 14.7	0.82
Age at onset of asthma, y	36.1 ± 20.1	32.6 ± 22.8	0.32
Body mass index, kg/m ²	22.5 ± 3.2	24.2 ± 4.7	0.07
History of smoking	26.8	17.4	0.19
Aspirin intolerance	12.5	20.7	0.36
Atopic dermatitis	22.0	25.4	0.84
Allergic rhinitis	61.0	69.1	0.35
Chronic rhinosinusitis with nasal polyps	43.9	39.7	0.72
Olfactory dysfunction	36.6	28.3	0.34
Poor adherence to the treatment	15.4	5.1	0.04
Daily dose of inhaled corticosteroids, µg [†]	273 ± 195	744 ± 292	<0.001
Patients treated with daily oral corticosteroids	0	37.8	<0.001
Patients treated with omalizumab	0	12.8	0.009
Laboratory measurements			
Eosinophils/µl of blood	421 ± 667	465 ± 537	0.71
Total serum IgE, IU/ml, median (interquartile range)	160 (71–550)	330 (136–658)	0.04
Atopic type	53.7	59.5	0.59
Pulmonary function (n = 173)			
VC, % predicted	98 ± 13	92 ± 19	0.03
FEV ₁ , % predicted	91 ± 15	80 ± 23	<0.001
FEV ₁ /FVC, %	69 ± 10	64 ± 14	0.01
Fractional exhaled nitric oxide, ppb (n = 80)	29 ± 32	49 ± 51	0.03
Asthma severity and quality of life scores			
Asthma Control Test	22.5 ± 3.2	18.9 ± 5.0	<0.001
Asthma Quality of Life Questionnaire	5.5 ± 1.0	4.7 ± 1.2	<0.001

Values are proportions of patients in each study groups or means ± SD if not otherwise specified.

IgE, immunoglobulin E; VC, vital capacity; FEV₁, Forced expiratory volume in 1 s; FVC, forced vital capacity.

[†] Dose of inhaled corticosteroids are shown as fluticasone propionate equivalent.

guidelines.² Table 1 compares the characteristics of 42 patients included in the GINA treatment steps 1 to 3 with those of 148 patients included in steps 4 and 5. The serum concentration of total IgE and fractional exhaled nitric oxide in the latter group were significantly higher, while VC, FEV₁, and the asthma control test and asthma quality of life questionnaire scores were significantly lower. The rate of patients with poor adherence to the treatment was lower in severe asthma group, and there were no differences between the 2 groups in sex distributions, age, body mass index, peripheral blood eosinophil counts, atopic status, and prevalence of comorbidity, including aspirin intolerance, atopic dermatitis, allergic rhinitis and chronic rhinosinusitis with nasal polyps.

Relationship between serum periostin concentrations and severity of asthma

The median serum periostin concentrations in the 190 asthmatic patients was 70.0 (54.0–93.5) ng/ml, versus 57.0 (39.0–63.0) ng/ml in the 11 healthy subjects ($P = 0.014$). There were no significant differences, however, in the serum periostin concentrations measured among patients in GINA step 1–3 [66.5 (51.0–87.0) ng/mL], step 4; 70.0 (57.0–97.0) ng/mL, and step 5; 72.0 (54.0–103.0) ng/mL (Fig. 1). Periostin concentrations ≥ 90 ng/mL, observed in 33% of the step 4 & 5 group, was found in only in 14% of the step 1–3 group ($P = 0.02$ compared to step 4 & 5 group) and none of the healthy controls ($P = 0.02$ compared to step 4 & 5 group), suggesting that a specific asthmatic phenotype(s) characterized by elevated serum periostin concentrations (“periostin-high” asthma) is more prevalent among patients requiring the most intensive treatment.

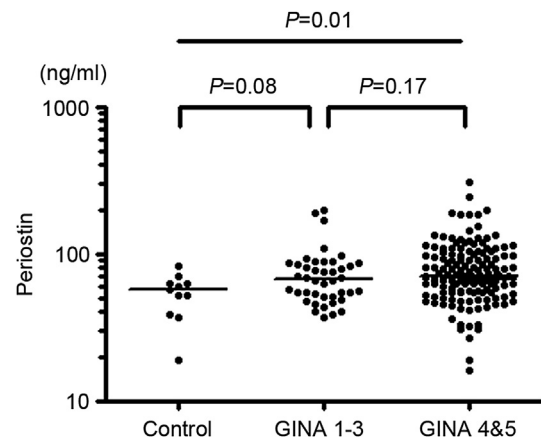


Fig. 1. Relationship between serum periostin concentrations and severity of asthma. The serum periostin concentrations in 11 healthy subjects 190 patients with asthma are shown. The patients with asthma were divided between GINA treatment steps 1–3 and step 4 & 5. Bars indicate median values.

High serum periostin concentrations indicate a specific asthmatic phenotype

To characterize the “periostin-high” phenotype of asthma, we divided the 190 asthmatic patients among tertiles according to the serum periostin concentrations (Table 2). The average age and age at onset of asthma were significantly older in the high-than in the low-periostin group, and the prevalence of late-onset asthma (age at onset ≥ 40 y) in high-periostin group (59.3%) was 1.7 times as high as that in low-periostin group (34.5%, $P = 0.009$). Furthermore, allergic rhinitis, olfactory dysfunction and aspirin-intolerance were more prevalent, and abnormalities of pulmonary function tests and peripheral eosinophil counts were significantly greater in the high-than the low-periostin group (Table 2). Finally, the serum concentrations of TH2 cytokines, IL-4 and IL-13, were higher in the high-periostin group, though the difference was of borderline statistical significance (Table 2). There was a weak to moderate correlation between serum periostin levels and peripheral blood eosinophilia ($\rho = 0.38$, $p < 0.0001$) and weak correlation with TH2 cytokine levels in serum ($\rho = 0.18$ – 0.21 , $p = 0.01$ – 0.03 , Supplementary Fig. 1). When the analysis was limited to the 148 patients included in the GINA step 4 and 5 group, the highest-periostin group was also older at the time of onset of asthma, was leaner, had a higher prevalence of nasal diseases, lower pulmonary functions, and higher serum TH2 cytokine concentrations and peripheral eosinophil counts (Supplementary Table 1).

Because high periostin concentrations were correlated with nasal disorders, such as allergic rhinitis, chronic rhinosinusitis with nasal polyps, and olfactory dysfunction (Supplementary Fig. 2), then we examined which component(s) of the disorders determined this relationship. Fig. 2 shows that the patients who suffered from both chronic rhinosinusitis with nasal polyps and olfactory dysfunction had the highest serum periostin concentrations ($P = 0.001$ compared with the patients without nasal disorder). FEV₁ and FEV₁/forced vital capacity (FVC) were lower among patients with high serum periostin concentrations (Table 2). We, therefore, performed single and multivariate analyses to examine whether serum periostin was correlated with obstructive pulmonary dysfunction, and found that log-transformed serum periostin concentrations were weakly correlated with FEV₁/FVC ($P = 0.03$; Table 3), but not with %predicted FEV₁ ($P = 0.27$). By multiple variable analysis, serum periostin concentration was marginally correlated with FEV₁/FVC independently of asthma duration or smoking history (Table 3).

Table 2

Characteristics of patients in the low, intermediate and high periostin groups.

	Periostin			<i>P</i> [†]
	Low (<i>n</i> = 63)	Intermediate (<i>n</i> = 64)	High (<i>n</i> = 63)	
Serum periostin, ng/ml, median (interquartile range)	49.0 (43.5–54.0)	70.0 (65.0–77.3)	109 (94.0–129.0)	
Demographic and clinical observations				
Men	44.4	39.1	49.2	0.72
Age, y	56.1 ± 15.0	60.6 ± 14.3	64.1 ± 13.4	0.002
Age at onset of asthma, y	29.4 ± 23.4	33.8 ± 24.0	36.9 ± 18.4	0.04
Early-onset asthma (age at onset < 16 y)	37.9	32.2	18.5	0.02
Late-onset asthma (age at onset ≥ 40 y)	34.5	47.5	59.3	0.009
Body mass index, kg/m ²	24.4 ± 5.3	24.0 ± 4.4	22.9 ± 3.2	0.23
History of smoking	16.4	19.0	23.7	0.59
Aspirin intolerance	11.5	18.3	27.1	0.04
Atopic dermatitis	16.4	3.3	24.1	0.36
Allergic rhinitis	57.4	68.3	76.3	0.03
Chronic rhinosinusitis with nasal polyps	31.7	42.4	48.3	0.09
Olfactory dysfunction	16.4	28.3	46.6	0.001
Poor adherence to the treatment	3.5	10.0	8.6	0.23
Daily dose of inhaled corticosteroids, µg [‡]	611 ± 348	638 ± 303	676 ± 356	0.31
Patients treated with daily oral corticosteroids	27.7	26.1	32.3	0.70
Patients treated with omalizumab	11.1	7.8	11.1	1.00
Laboratory measurements				
Eosinophils/µl of blood	319 ± 490	469 ± 629	584 ± 540	<0.001
Total serum IgE, IU/ml, median (interquartile range)	250 (73–654)	325 (98–636)	313 (134–643)	0.34
Atopic type	62.9	59.4	52.4	0.28
Interleukins (IL)				
Serum IL-4, pg/dl	11.7 ± 7.6	14.3 ± 8.9	15.3 ± 9.1	0.06
Serum IL-5, pg/dl	34.0 ± 18.9	40.1 ± 20.6	41.0 ± 22.8	0.22
Serum IL-13, pg/dl	22.0 ± 22.0	20.2 ± 7.5	30.4 ± 44.1	0.06
Pulmonary function (<i>n</i> = 173)				
VC, % predicted	92.8 ± 16.1	96.2 ± 20.2	90.5 ± 16.5	0.32
FEV ₁ , % predicted	83.3 ± 22.7	87.5 ± 22.9	76.1 ± 20.0	0.07
FEV ₁ /FVC, %	67.2 ± 14.2	67.5 ± 11.7	61.4 ± 13.4	0.02
Fractional exhaled nitric oxide, ppb (<i>n</i> = 80)	45.9 ± 61.7	40.6 ± 35.9	49.3 ± 46.9	0.50
Computed tomography (<i>n</i> = 55)				
Wall area, %	59.1 ± 9.7	57.7 ± 7.0	56.9 ± 6.8	0.51
Asthma severity and quality of life scores				
Asthma Control Test	19.7 ± 4.7	19.3 ± 5.3	20.2 ± 4.6	0.53
Asthma Quality of Life Questionnaire	4.9 ± 1.2	4.8 ± 1.3	4.8 ± 1.3	0.88

Values are proportions of patients in each study groups or means ± SD if not otherwise specified.

IgE, immunoglobulin E; VC, vital capacity; FEV₁, Forced expiratory volume in 1 s; FVC, forced vital capacity.[†] Low versus High periostin group.[‡] Dose of inhaled corticosteroids are shown as fluticasone propionate equivalent.

Discussion

Since asthma is a heterogeneous disease, its treatment, especially when severe, should be based on the specific molecular mechanism identified in each individual patient. The serum periostin concentration was expected to be a reliable surrogate marker of IL-13 activity *in vivo* and of persistent eosinophilic inflammation in the airways. The present study adds further evidence that serum periostin is clinically useful, by showing that its concentration is correlated with a specific phenotype of asthma, instead of with its severity.

Periostin is localized with other matricellular proteins in the subepithelial layer of the airways. Its elevated expression in bronchial epithelial cells is related to subepithelial fibrosis of the airways.⁶ Furthermore, the serum periostin concentrations correlate with an annual decline in FEV₁, independently of the severity of asthma or smoking history, in asthmatics treated with inhaled corticosteroids.¹⁰ Therefore, periostin seems to contrast with other biomarkers of asthma, such as YKL-40 and C-reactive protein, which reflect airway inflammation, but not a specific phenotype such as a rapid deterioration of pulmonary function.¹⁹ Our observation that patients with high serum periostin concentrations had low FEV₁ and FEV₁/FVC in spite of shorter duration of asthma

confirms that periostin is a biomarker of rapid decline in pulmonary function. However, we could not show a relationship between serum periostin concentrations and airway remodelling assessed by the airway wall thickness on computed tomography morphometry. That relationship will require further study.

The “high-periostin” phenotype identified in our study, i.e. late-onset asthma with eosinophilia and concomitant nasal disorders, corresponds to the phenotypes/endotypes proposed by other researchers. A cluster analysis of severe asthma suggested the presence of an inflammation-predominant phenotype, characterized by a later onset of the disease with active eosinophilic inflammation.²⁰ Another study also described a population of patients with severe, adult-onset asthma, who were more likely to be non-atopic, associated with increased concentrations of exhaled nitric oxide and sputum eosinophils, and in whom nasal symptoms and polyposis were more prevalent.²¹ This late-onset, hypereosinophilic asthma is also considered a specific endotype.²²

We found that high concentrations of serum periostin were correlated with other nasal disorders, such as allergic and non-allergic rhinosinusitis. Among the nasal disease manifestations, the combination of chronic rhinosinusitis with nasal polyps and olfactory dysfunction was most prominently correlated with high concentrations of serum periostin. The combination of nasal polyps

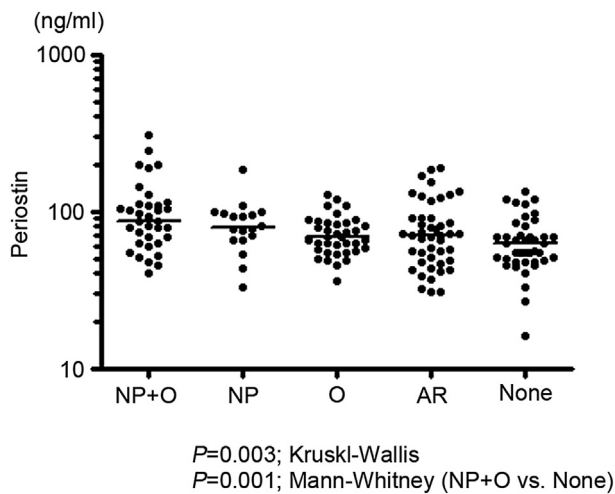


Fig. 2. Relationships between serum periostin concentrations and concomitant nasal disorders. The serum periostin concentrations in patients with versus without concomitant nasal disorders are compared. NP + O, chronic rhinosinusitis with nasal polyps + olfactory dysfunction; NP, chronic rhinosinusitis with nasal polyps without olfactory dysfunction; O, olfactory dysfunction without chronic rhinosinusitis with nasal polyps; AR, allergic rhinitis alone. Bars indicate median values. Kruskal–Wallis test and Mann–Whitney test were used to compare the groups. $P = 0.003$; Kruskal–Wallis, $P = 0.001$; Mann–Whitney (NP + O vs. none).

Table 3
Relationships between serum periostin concentrations and pulmonary function.

	FEV ₁ /FVC	
	β	P
Analysis		
<i>Single variable</i>		
Serum periostin concentration [†]	−0.16	0.03
<i>Multiple variable</i>		
Unadjusted		
Serum periostin concentration [†]	−0.15	0.05
Disease duration	−0.31	<0.001
History of smoking	−0.16	0.04
Adjusted for age and sex		
Serum periostin concentration [†]	−0.06	0.42
Disease duration	−0.27	<0.001
History of smoking	−0.03	0.70

FEV₁, Forced expiratory volume in 1 s; FVC, forced vital capacity.

[†] Log-transformed.

and hyposmia/anosmia is observed in patients with chronic eosinophilic rhinosinusitis, often complicated by peripheral blood eosinophilia and aspirin-intolerant asthma.²³ Therefore, a high proportion of our patients presenting with both chronic rhinosinusitis with nasal polyps and olfactory dysfunction might have suffered from chronic eosinophilic rhinosinusitis, though this was not confirmed by pathologic studies. Periostin mRNA is increasingly expressed in the nasal mucosa of patients presenting with chronic eosinophilic rhinosinusitis with nasal polyps.^{24,25} Therefore, the concentrations of serum periostin may reflect an increased production of this molecule in both the upper and the lower airways.

It has been considered that early-onset atopic asthma is a TH2-related disease,¹ however, our study showed that the high serum periostin concentrations were not correlated with serum concentrations of IgE or atopic status, and rather associated with late-onset asthma. It has been reported that the expression of periostin is decreased by corticosteroids,^{6,7} therefore, the periostin concentrations in early-onset atopic asthma might have been decreased by corticosteroid. The reason why the concentrations of periostin remained elevated despite corticosteroids in adult-onset

eosinophilic asthma has not been clear yet. In *in vitro* experiments, corticosteroids completely inhibited the IL-4/13-induced periostin production in fibroblasts, and enhanced it in microvascular endothelial cells, however, the TGF- β -induced production of periostin in fibroblasts is resistant to corticosteroids,²⁶ suggesting that the site or microenvironment of periostin synthesis might be different in early-versus late-onset asthma. Serum periostin levels, therefore, can be a useful biomarker to identify specific phenotypes of severe asthma independently of atopic status.

Study limitations

The diagnoses of concomitant disorders, such as aspirin-intolerant asthma, atopic dermatitis, allergic rhinitis and chronic rhinosinusitis with nasal polyps were based on the patients' answers to the questionnaire, not on objective measurements from challenge tests, or radiographic and pathological examinations. Therefore, patients with asymptomatic concomitant diseases may have been missed in the analysis. Second, since this study was based on a cross-sectional analysis, we could not determine whether the concentrations of periostin in serum were stable through the course of the disease, or varied according to its control or therapeutic interventions. Third, we have no data whether serum periostin levels can be influenced by age or sex, therefore, the difference in serum periostin levels between healthy subjects and asthmatic patients may have been compromised by the difference in age and gender distribution.

In conclusion, periostin is a biomarker that reliably identifies a TH2-related asthma, late-onset, eosinophilic, and often complicated with declining pulmonary function and nasal diseases, chronic eosinophilic rhinosinusitis in particular.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.alit.2014.07.003>.

Conflict of interest

KI received research funding from Shino-Test Corporation. KA received research funding from Astellas Pharma; honoraria as lecture fees from Astellas Pharma, GSK, and MSD. TB received research funding from GSK. The rest of the authors have no conflict of interest.

Authors' contributions

MM and Hirk equally contributed to this work.

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