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To cite this article: Kentaro Takahashi, Kazuyuki Meguro, Hirotohi Kawashima, Daisuke Kashiwakuma, Shin-ichiro Kagami, Shoichiro Ohta, Junya Ono, Kenji Izuhara & Itsuo Iwamoto (2018): Serum periostin levels serve as a biomarker for both eosinophilic airway inflammation and fixed airflow limitation in well-controlled asthmatics, Journal of Asthma, DOI: [10.1080/02770903.2018.1455855](https://doi.org/10.1080/02770903.2018.1455855)

To link to this article: <https://doi.org/10.1080/02770903.2018.1455855>



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Published online: 12 Apr 2018.



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Serum periostin levels serve as a biomarker for both eosinophilic airway inflammation and fixed airflow limitation in well-controlled asthmatics

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ABSTRACT

Objective: Periostin, a matricellular protein, is produced from airway epithelial cells and lung fibroblasts by IL-13. It has been suggested that periostin is involved in allergic inflammation and fibrosis. However, the usefulness of serum periostin measurement in the assessment of airway inflammation and remodeling and management of asthmatic patients is still debated. We aimed to determine whether serum periostin levels reflect eosinophilic airway inflammation and airway remodeling in asthma. **Methods:** We examined the relationship of serum periostin levels with clinical features, biomarkers for eosinophilic airway inflammation, fraction of exhaled nitric oxide (FeNO) levels and blood eosinophil counts, and pulmonary functions in 235 well-controlled asthmatic patients on inhaled corticosteroids (ICS) treatment. **Results:** Serum periostin levels were positively correlated with blood eosinophil counts (%) and age ($r = 0.36$ and 0.23 , respectively), and were negatively correlated with body weight and FEV₁/FVC (%) ($r = -0.24$ and -0.23 , respectively) in well-controlled asthmatic patients on ICS treatment (daily dose of 453 μg equivalent to fluticasone propionate). Blood eosinophil counts and serum periostin levels were similarly associated with increased FeNO levels (≥ 40 ppb) in the asthmatics. Serum periostin levels were better associated with fixed airflow limitation (FEV₁/FVC ratio $< 70\%$) than FeNO levels, blood eosinophil counts or total IgE levels in the asthmatics. Multivariate analysis showed that fixed airflow limitation was significantly associated with high serum periostin levels (≥ 97 ng/ml) (Odds ratio 3.2). **Conclusions:** Serum periostin levels serve as a biomarker for both eosinophilic airway inflammation and fixed airflow limitation in well-controlled asthmatics on ICS treatment.

ARTICLE HISTORY

Received 7 December 2017
Revised 11 March 2018
Accepted 19 March 2018

KEYWORDS

Biomarkers;
control/management;
mechanisms

Introduction

Asthma is characterized mainly by eosinophilic airway inflammation with airway obstruction and airway hyper-reactivity (1–3), although other phenotypes have been proposed (4, 5). Airway eosinophilia is associated with the severity (6,7) and exacerbations (8–10) of asthma and fixed airflow limitation through airway remodeling (11). Eosinophilic airway inflammation is elicited by Th2 cells and their cytokines IL-4, IL-5, and IL-13 (1–3). Biomarkers for eosinophilic airway inflammation in asthma have been intensely investigated to assess the magnitude of airway inflammation and asthma control. Peripheral blood eosinophilia is mediated by IL-5 (12) and is well correlated with airway eosinophilia (13, 14), and thus is often used as a surrogate marker for eosinophilic airway inflammation (12). The fraction of exhaled nitric oxide (FeNO) is also considered to be a surrogate marker for eosinophilic airway inflammation and is used for monitoring asthma control (15) because the production of NO is increased by IL-13 in airway epithelial cells (16,17).

Periostin is a 90-kDa matricellular protein originally isolated from osteoblasts (18) and promotes cell adhesion and spreading of fibroblasts and epithelial cells (18, 19). Periostin is upregulated in airway epithelial cells collected from asthmatic patients as compared with those of healthy subjects and is downregulated after inhaled corticosteroid (ICS) treatment (20). Periostin is secreted from airway epithelial cells by the stimulation with IL-13 (20) and is also induced by IL-4 and IL-13 in lung fibroblasts (21). Secreted periostin induces the production of type I collagen by lung fibroblasts (19). Thus, it is suggested that periostin is involved in airway remodeling in asthma (19,21). It has also been shown that the effectiveness of anti-IL-13 antibody treatment is greater in asthmatic patients with high serum periostin levels than in patients with low periostin levels (22), suggesting that serum periostin level may be a surrogate marker for IL-13-mediated eosinophilic airway inflammation in asthma. Periostin is therefore expected as a biomarker for the treatment of asthma in view of precision medicine

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from recent bioinformatics approaches (23). Periostin is also involved in allergic inflammatory responses in the skin and airways of mice (24,25). However, the usefulness of serum periostin measurement and its relationship with other Th2-type biomarkers in the assessment of airway inflammation and remodeling and management of patients with asthma are still unknown. Specifically, although it has been shown that serum periostin levels are a useful biomarker for eosinophilic airway inflammation in uncontrolled asthmatic patients on ICS treatment (22,26,27), it is largely unknown whether serum periostin levels are a useful biomarker in the assessment of airway inflammation and remodeling of well-controlled asthmatics on ICS treatment.

In this study, we examined the relationship of serum periostin levels with clinical features and biomarkers for eosinophilic airway inflammation, FeNO levels, and blood eosinophil counts, in stable asthmatics controlled by ICS treatment. Our results suggest that serum periostin levels may serve as a biomarker for both eosinophilic airway inflammation and fixed airflow limitation in well-controlled asthmatics on ICS treatment.

Methods

Patients

This study was a single center retrospective evaluation of 235 adult patients with asthma who were well controlled by ICS treatment. The patients were diagnosed having asthma according to the American Thoracic Society criteria (28). Patients were seen regularly (at a 4 to 8-week interval) by allergists to assess asthma control and were received routine clinical management. These patients were well controlled by their maintenance doses of ICS (Table 1) on the basis of GINA2012 criteria and Japanese asthma guideline 2014 criteria (29,30), with no asthma symptoms or reliever use for the previous 1 month. Some patients were also taking, in addition to ICS, long-acting β_2 agonists, leukotriene receptor antagonists, or/and theophyllines (Table 1). We collected detailed patients' characteristics, asthma control status, peripheral blood eosinophil counts, fraction of exhaled nitric oxide (FeNO) values, and pulmonary function values (Table 1).

Patients were excluded if they had asthma exacerbations in the past 1 year (29,30), respiratory tract infections in the past 1 month, smoking history of over 10 pack-year, smoking history in the past 3 months, or other diseases which includes pulmonary, infectious, autoimmune or malignant diseases, or pregnancy. This study was approved by the Ethics Committee of Asahi General Hospital (No. 2013052114) and was performed in accordance with the principles of the Declaration of Helsinki.

Table 1. Demographic and clinical characteristics of 235 asthmatic patients.

	Value
Age (years)	46 $\pm$ 18
Sex (male/female, <i>n</i>)	66 / 169
Disease duration (years)	19 $\pm$ 14
Aspirin-intolerant asthma (%)	6.8
Smoking (pack-year)	0.78 $\pm$ 2.09
Daily ICS dose (equivalent to FP, μ g)	453 $\pm$ 173
ICS use (<i>n</i> (%))	235 (100.0)
Leukotriene receptor antagonist (<i>n</i> (%))	92 (39.1)
Theophylline (<i>n</i> (%))	82 (34.8)
Long-acting β_2 agonist (<i>n</i> (%))	22 (9.3)
Systemic corticosteroids (<i>n</i> (%))	4 (1.7)
FEV ₁ (% predicted)	92 $\pm$ 16
FEV ₁ /FVC (%)	78 $\pm$ 10
FeNO (ppb)	48 $\pm$ 44
Blood eosinophil count (%)	4.8 $\pm$ 3.7
Total IgE (IU/mL)	446 $\pm$ 669
Periostin (ng/mL)	88 $\pm$ 32

Note: Plus-minus values are means $\pm$ SD.

ICS: inhaled corticosteroids, FP: fluticasone propionate, FEV₁: forced expiratory volume in one second, FVC: forced vital capacity, FeNO: fraction of exhaled nitric oxide.

Spirometry and FeNO measurements

Spirometry was performed with an electrical spirometer (Autospirometer System 21, Minato Medical, Osaka, Japan) according to the American Thoracic Society/European Respiratory Society guideline (31). Daily ICS, long-acting β_2 agonists, leukotriene receptor antagonists, or sustained-release theophyllines were not withdrawn before spirometry. The patients routinely underwent spirometry measurements twice a year when they were in stable conditions and without wheezing on auscultation.

FeNO measurements were performed with an NO analyzer (Sievers NOA 280i, GE Analytical instruments, Boulder, CO, USA) according to the American Thoracic Society guideline (15).

Fixed airflow limitation was defined as a postbronchodilator FEV₁/FVC ratio <70%, according to the previous reports (32,33).

Blood analysis

Peripheral blood eosinophil counts (%), serum total IgE levels, and specific IgE antibodies were measured at clinical laboratory in our hospital. The residual serum samples were frozen at -80°C until assay of serum periostin.

Measurement of serum periostin

Serum periostin levels were measured with a sandwich enzyme-linked immunosorbent assay (Shino-Test Corp., Kanagawa, Japan) using 2 rat anti-human periostin mAbs (clones no. SS18A and SS17B), as previously described (34). Briefly, 100- to 200-fold diluted serum samples or

recombinant periostin standards were added into the ELISA plates preincubated with SS18A mAb and incubated for 18 h at 25°C. After washing, the peroxidase labeled SS17B mAb was then added followed by incubation for 90 min at 25°C. Periostin concentrations in the serum were calculated simultaneously using the recombinant periostin proteins. The assay was performed in duplicate. Serum periostin levels were also measured in 111 healthy, never-smoking subjects.

Statistical analysis

Statistical analysis was performed using JMP software version 9.0 (SAS Institute Japan, Tokyo, Japan) or R version 3.3.1 (R Core Team, 2016). Data were analyzed using Mann-Whitney U test and Fisher's exact test for comparisons of continuous and dichotomous variables, respectively. Statistical correlations between serum periostin levels and respective variables were estimated with Pearson's correlation coefficients. Multiple logistic regression analysis was performed with variables with $p < 0.05$ on univariate analysis, except for disease duration because of its strong correlation with age. Receiver operating characteristic (ROC) curve analysis was performed to determine the association between increased FeNO levels (≥ 40 ppb) versus serum periostin levels, blood eosinophil counts (%), and total IgE levels and also between fixed airflow limitation (FEV_1/FVC ratio $< 70\%$) versus serum periostin levels and other variables. Data are summarized as means $\pm$ SD. P values < 0.05 were considered significant.

Results

Correlations between serum periostin levels and other clinical findings

Table 1 shows the characteristics of asthmatic patients in this study. A total of 235 patients (66 males and 169 females) were well controlled by ICSs (daily dose of 453 ± 173 μ g (mean $\pm$ SD) equivalent to fluticasone propionate (FP)) according to GINA2012 criteria and Japanese asthma guideline 2014 criteria (29,30). Serum periostin levels of these well-controlled asthmatics were 88 ± 32 ng/ml (Table 1) and were significantly higher than those in healthy, never-smoking subjects (60 ± 25 ng/ml, $n = 111$, $p < 0.0001$) (Supplementary Table S1). The correlations between serum periostin levels and clinical findings were then assessed. Serum periostin levels were positively correlated with peripheral blood eosinophil counts (%) and age ($r = 0.36$, $p < 0.0001$, and $r = 0.23$, $p < 0.001$, respectively), and were negatively correlated with body weight and FEV_1/FVC (%) ($r = -0.24$, $p < 0.001$ and $r =$

Table 2. Correlations between serum periostin levels and respective variables in well-controlled asthmatics.

	r	P value
Age (years)	0.2347	<0.001
Height (cm)	− 0.0578	NS
Body weight (kg)	− 0.2399	<0.001
Body mass index (kg/m²)	− 0.2304	<0.001
Disease duration (years)	− 0.0585	NS
Smoking (pack-year)	− 0.1784	<0.01
Daily ICS dose (equivalent to FP, μ g)	− 0.0056	NS
FEV ₁ (% predicted)	− 0.1021	NS
FEV₁/FVC (%)	− 0.2250	<0.001
FeNO (ppb)	0.1409	<0.05
Blood eosinophil count (%)	0.3624	<0.0001
Total IgE (IU/mL)	− 0.0129	NS

Note: Bold indices have a correlation with serum periostin levels ($r > 0.2$ or < -0.2).

NS: not significant.

ICS: inhaled corticosteroids, FP: fluticasone propionate, FEV₁: forced expiratory volume in one second, FVC: forced vital capacity, and FeNO: fraction of exhaled nitric oxide.

−0.23, $p < 0.001$, respectively) (Table 2). Periostin levels were not significantly correlated with disease duration, height, smoking history, or daily ICS dose.

Serum periostin levels and blood eosinophil counts serve as a biomarker for eosinophilic airway inflammation in well-controlled asthmatics

To determine whether serum periostin levels reflect eosinophilic airway inflammation in asthma, we assessed the association between the fraction of exhaled nitric oxide (FeNO), a surrogate marker for eosinophilic airway inflammation (15), and other Th2-type biomarkers, serum periostin levels, blood eosinophil counts, and total IgE levels, by constructing ROC curves (Figure 1). Blood eosinophil counts (%) and serum periostin levels were similarly associated with increased FeNO levels (≥ 40 ppb). Areas under the curves (AUC) of blood eosinophil counts (%), serum periostin levels, and total IgE levels were 0.70, 0.65, and 0.54, respectively. These results suggest that serum periostin levels as well as blood eosinophil counts may serve as a biomarker for eosinophilic airway inflammation in well-controlled asthmatics on ICS treatment.

Increased serum periostin levels are associated with fixed airflow limitation in well-controlled asthmatics

We assessed the relation between serum periostin levels and other variables and fixed airflow limitation defined as a postbronchodilator FEV_1/FVC ratio $< 70\%$. Diagnostic performance of serum periostin levels, FeNO levels, blood eosinophil counts, and total IgE levels to predict fixed airflow limitation was examined by constructing ROC curves. ROC curve analysis showed that serum periostin

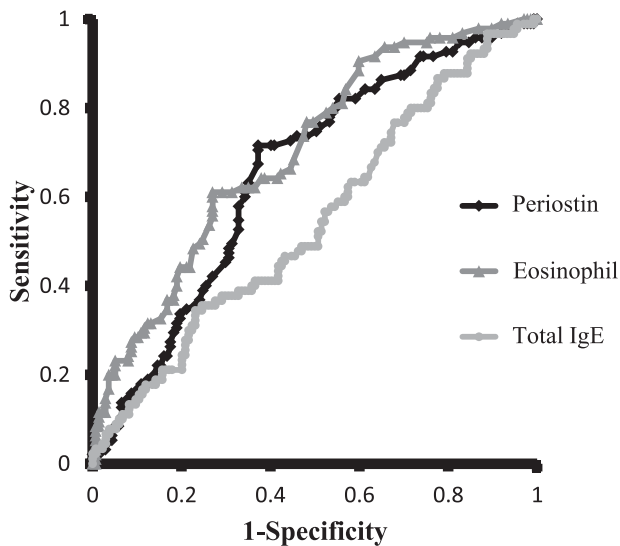


Figure 1. Serum periostin levels are a useful biomarker for eosinophilic airway inflammation (FeNO levels ≥ 40 ppb) in well-controlled asthmatics. ROC curve analysis was performed for blood eosinophil counts (gray triangle), serum periostin levels (black rhombus), and total IgE levels (gray circle) to predict the possible presence of eosinophilic airway inflammation (FeNO levels ≥ 40 ppb). The areas under the curves (AUC) were 0.70, 0.65, and 0.54, respectively.

levels (AUC; 0.69) were better associated with fixed airflow limitation than FeNO levels, blood eosinophil counts (%) or total IgE levels (AUC; 0.52, 0.51, and 0.44, respectively), and that cut-off values were serum periostin 97 ng/mL, FeNO 38.8 ppb, blood eosinophil counts 3.4%, and total IgE 205 IU/mL, respectively (Figure 2). When serum periostin cut-off value of 97 ng/mL was used, the sensitivity and specificity were 0.62 and 0.73, respectively. Periostin high (≥ 97 ng/mL) patients were significantly older and showed older age of onset and higher rate of aspirin-intolerant asthma as compared with those of periostin low (< 97 ng/mL) patients (data not shown).

We next performed univariate analysis, using these cut-off values of variables. There were significant associations between fixed airflow limitation and age, onset age, disease duration, non-atopic asthma, aspirin-intolerant asthma, history of admission due to asthma exacerbations, smoking history, severe asthma (daily ICS dose over 500 μ g equivalent to FP), and high serum periostin (≥ 97 ng/mL) (Table 3). However, blood eosinophil counts $\geq 3.4\%$, FeNO levels ≥ 38.8 ppb, or total IgE levels ≥ 205 IU/mL were not significantly associated with fixed airflow limitation. Multiple logistic regression analysis showed that fixed airflow limitation was significantly associated with three clinical features of asthma, including history of admission due to asthma exacerbations (OR 10.4), high serum periostin levels (≥ 97 ng/mL) (OR 3.9), and aspirin-intolerant asthma (OR 4.3) (Table 3). These results suggest that serum periostin

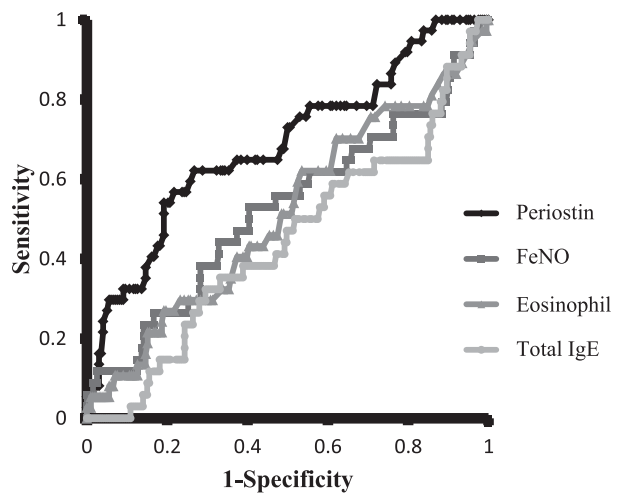


Figure 2. Serum periostin levels are a useful biomarker for fixed airflow limitation (FEV₁/FVC ratio $< 70\%$) in well-controlled asthmatics. ROC curve analysis shows that serum periostin levels (black rhombus) (AUC; 0.69) are better associated with fixed airflow limitation (FEV₁/FVC ratio $< 70\%$) than FeNO levels (gray square), blood eosinophil counts (gray triangle), or total IgE levels (gray circle) (AUC; 0.52, 0.51, and 0.44, respectively). The cut-off value of serum periostin levels for fixed airflow limitation was 97 ng/mL (sensitivity 0.62 and specificity 0.73).

levels, but not blood eosinophil counts or FeNO levels, may serve as a biomarker for fixed airflow limitation in well-controlled asthmatics on ICS treatment.

Discussion

In this study, we show that serum periostin levels as well as blood eosinophil counts serve as a biomarker for eosinophilic airway inflammation in well-controlled asthmatics on ICS treatment. We found that, by ROC curve analysis, blood eosinophil counts and serum periostin levels were similarly associated with increased FeNO levels (≥ 40 ppb), which imply the presence of eosinophilic airway inflammation (15), in well-controlled asthmatic patients on ICS treatment (daily dose of 453 μ g equivalent to FP) (Figure 1). Second, we show that serum periostin levels, but not blood eosinophil counts or FeNO levels, serve as a biomarker for fixed airflow limitation in asthma. ROC curve analysis showed that serum periostin levels were better associated with fixed airflow limitation (FEV₁/FVC ratio $< 70\%$) than FeNO levels, blood eosinophil counts, or total IgE levels in the asthmatics (Figure 2). Multivariate analysis showed that fixed airflow limitation was significantly associated with high serum periostin levels (≥ 97 ng/mL) (OR 3.2) (Table 3). These results suggest that serum periostin levels may serve as a biomarker for both eosinophilic airway inflammation and fixed airflow limitation in well-controlled asthmatics on ICS treatment.

Table 3. Univariate and multivariate analyses for fixed airflow limitation in well-controlled asthmatics.

	Univariate			Multivariate		
	Odds ratio	95% CI	P value	Odds ratio	95% CI	P value
Age*	—	—	<0.0001	1.083	1.034–1.133	0.0007
Sex (female)	0.796	0.310–1.872	0.7370	—	—	—
Body weight*	—	—	0.0226	0.986	0.932–1.042	0.6139
Disease duration	—	—	0.0004	—	—	—
Aspirin-intolerant asthma*	11.64	3.511–42.35	<0.0001	4.317	1.028–18.14	0.0458
Non-atopic asthma*	2.417	1.075–5.392	0.0246	1.362	0.377–4.929	0.6375
Chronic sinusitis	1.633	0.701–3.678	0.2217	—	—	—
Smoking (pack-year)*	—	—	0.0182	0.476	0.076–2.983	0.4278
History of admission*	6.362	2.723–16.27	<0.0001	10.35	3.320–32.25	0.0001
Severe asthma**	3.042	1.399–6.694	0.0034	3.039	0.987–9.352	0.0527
FeNO ≥ 38.8 (ppb)*	1.656	0.748–3.698	0.1913	1.055	0.347–3.210	0.9248
Blood eosinophils ≥ 3.4 (%)*	1.424	0.658–3.179	0.3718	0.851	0.264–2.737	0.7860
Total IgE ≥ 205 (IU/mL)*	0.930	0.419–2.065	0.8548	1.162	0.340–3.978	0.8106
Periostin ≥ 97 (ng/mL)*	4.461	2.030–10.13	<0.0001	3.240	1.025–10.24	0.0453

Note: In univariate analysis, data were analyzed using Mann-Whitney U test and Fisher's exact test for comparisons of continuous and dichotomous variables, respectively.

Multiple logistic regression analysis was performed with variables with $p < 0.05$ on univariate analysis and variables with asterisks.

*Severe asthma was defined as the patients taking daily ICS dose over 500 μg equivalent to fluticasone propionate.

Bold indices are significantly associated with fixed airflow limitation ($p < 0.05$).

CI: confidence interval.

Periostin is produced from airway epithelial cells and lung fibroblasts by IL-13 (20,21). It has been shown that periostin expression is increased in airway epithelial cells from asthmatic patients as compared with those of healthy subjects (4,20) and that increased periostin expression is significantly associated with increased expression of IL-13 and IL-5 in the airways, blood and airway eosinophilia, airway hyperreactivity, and subepithelial thickness (4). Furthermore, it is suggested that serum periostin levels may be a surrogate marker for IL-13-mediated eosinophilic airway inflammation in uncontrolled asthmatic patients on ICS treatment (daily dose of 580 μg equivalent to FP)(22). Therefore, our results add to the evidence that serum periostin levels serve as a biomarker for eosinophilic airway inflammation in well-controlled asthmatics even on ICS treatment (Figure 1), although ICS treatment could reduce periostin production in the airways (20,35).

Our findings suggest that blood eosinophil counts and serum periostin levels both serve as a noninvasive biomarker for eosinophilic airway inflammation in well-controlled asthmatics on ICS treatment, as evidenced by the similar associations of these parameters with increased FeNO levels in the asthmatics (Figure 1). Recently, Jia et al. (26) reported that serum periostin levels were a better biomarker for airway eosinophilia in uncontrolled severe asthmatics despite maximal ICS treatment (daily dose of ≥ 1000 μg equivalent to FP) than blood eosinophil counts or FeNO levels. The difference in the usefulness of blood eosinophil counts as a biomarker between our study and Jia's study (26) might be explained by the difference in the severity of asthma and daily ICS doses in the two patient populations. Our

patients were well-controlled by medium doses of ICS (Table 1). Because serum periostin levels may fairly reflect IL-13-mediated eosinophilic airway inflammation (22) and IL-13 might be involved in corticosteroid-resistant asthma (36,37), whereas because blood eosinophil counts are dependent mainly on IL-5 (12) and generally sensitive to ICS treatment, IL-13-mediated eosinophilic airway inflammation may still exist in corticosteroid-resistant asthmatics of Jia's study. In addition, because it has also been shown that periostin is involved in the amplification and persistence of eosinophilic inflammation (24), the increase in serum periostin levels may reflect this effect of periostin in eosinophilic airway inflammation in asthma.

We also show that serum periostin levels, but not blood eosinophil counts or FeNO levels, serve as a biomarker for fixed airflow limitation in well-controlled asthmatics on ICS treatment. We found that fixed airflow limitation was significantly associated with high serum periostin levels ($\geq 97\text{ng/ml}$) (OR 3.2) in the asthmatics (Figure 2 and Table 3). We also found that fixed airflow limitation was significantly associated with clinical features of severe asthma, that is, history of admission due to asthma exacerbations (OR 10.4) and aspirin-intolerant asthma (OR 4.3) (Table 3). Our findings of the association of serum periostin levels with fixed airflow limitation in asthma are in line with the recent findings of other studies (38,39). Kanemitsu et al. (38) showed that high serum periostin levels (≥ 95 ng/mL) were significantly associated with greater annual decline in FEV₁ in well-controlled asthmatics on ICS treatment (daily ICS dose 525 μg equivalent to FP). Bobolea et al. (39) also reported that periostin levels in sputum were increased in severe refractory eosinophilic asthmatics (daily ICS dose ≥ 1000 μg

equivalent to FP) with fixed airflow limitation (FEV_1/FVC ratio $<70\%$) as compared with those with reversible airflow limitation. They also found an inverse correlation between sputum periostin levels and FEV_1/FVC ratios. Previous studies also demonstrated that periostin expression was increased in the subepithelial fibrosis region of asthmatic patients (20,21). Thus, our results indicate that serum periostin levels serve as a biomarker for airway remodeling proceeding to fixed airflow limitation in well-controlled asthmatics on ICS treatment.

Several possibilities exist to explain the dissociation between serum periostin levels and blood eosinophil counts or FeNO levels as a biomarker for fixed airflow limitation in asthmatics on ICS treatment (Figure 1 and Table 3). First, because periostin is a matricellular protein and is thought to be involved in cell division and adhesion and fibrosis (18,19), serum periostin levels may reflect increased periostin itself in the airways. Second, because it has been shown that IL-13 is involved in subepithelial fibrosis of asthmatics (40,41), serum periostin levels may be a more precise surrogate marker for IL-13-dependent events including airway remodeling than that of IL-5-dependent blood eosinophilia. Third, because IL-13 has also been suggested to be involved in corticosteroid-resistance in asthma (36,39), increased serum periostin levels may reflect corticosteroid-resistance in asthma, leading to airway remodeling.

Recent studies also showed the weak association between serum periostin levels and blood eosinophil counts and FeNO levels in asthmatics (35,42–44), although there are some differences in the findings between those studies and this study. James et al. showed that serum periostin levels were positively correlated with FeNO levels and urinary eosinophil-derived neurotoxin in population-based, self-reported asthmatic patients (predominantly mild asthmatics, about one-third of patients reported ICS use in the past week), and were inversely correlated with FEV_1 in the asthmatics (42). On the other hand, they found no difference in serum periostin levels between the asthmatics and healthy subjects (42). Similar serum periostin levels between the asthmatics and healthy subjects might be due to milder airway inflammation and greater BMI in their study. Fingleton et al. also found the weak correlations between serum periostin levels and blood eosinophil counts and FeNO levels in the asthmatics, about 50% of whom used ICS (35). Wagener et al. reported that there was a weak but significant correlation between serum periostin levels and sputum eosinophil counts in adult asthmatics treated with a median dose of 500 μ g equivalent to FP, whereas they found that serum periostin levels were not able to distinguish eosinophilic from noneosinophilic airway inflammation by ROC analysis using sputum eosinophil

counts (43). The difference in diagnostic power of serum periostin levels for eosinophilic airway inflammation by ROC analysis between their study and our study might be due to the differences in the parameters used for eosinophilic airway inflammation (sputum eosinophilia versus FeNO levels), the degree of airway inflammation decrement by ICS (20,35), and /or constitutional factors such as BMI. In another study, Johansson et al. found that serum periostin levels correlated with FeNO levels and blood eosinophil counts in severe asthmatics, but not in nonsevere asthmatics (44). Intriguingly, they also found that serum periostin levels were not significantly different among the groups with severe, nonsevere, and no asthma (44).

There are some limitations in this study. First, we did not measure sputum eosinophil counts that directly reflect the presence of eosinophilic airway inflammation. Instead we performed noninvasive FeNO analysis for the magnitude of possible eosinophilic airway inflammation (15). Second, our finding that fixed airflow limitation was associated with high serum periostin levels was based on a cross-sectional study. To confirm this, it is preferable to study the association between serum periostin levels and a yearly decline in FEV_1 in a prospective study. Despite the limitations, our findings of serum periostin levels would be applicable to most patients with asthma on ICS treatment in a real world situation to evaluate the future risks for fixed airflow limitation.

Conclusions

In summary, we have shown that serum periostin levels may serve as a biomarker for both eosinophilic airway inflammation and fixed airflow limitation in well-controlled asthmatics on ICS treatment, whereas blood eosinophil counts also serve as a useful biomarker for eosinophilic airway inflammation in the asthmatics on ICS treatment.

Declaration of interest

Kenji Izuhara received research funding associated with this study from Chugai Pharmaceutical Co. Ltd. and Shino-test Co. Ltd. The rest of the authors have no conflict of interest to declare.

Acknowledgements

We thank Dr. K. F. Chung for valuable discussion.

Funding

This work was supported by the Chugai Pharmaceutical Co. Ltd., Research funding; Shino-test Co. Ltd., Research funding.

Supplemental Information

Supplemental data for this article can be accessed at:
<https://doi.org/10.1080/02770903.2018.1455855>.

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Supplementary Table S1.

Demographics and serum periostin levels of 204 healthy subjects.

	Value
Age (years)	48 ± 16
Sex (male/female, n)	132 / 72
Periostin (ng/mL)	57 ± 24 (n=204)
Periostin in smokers (ng/mL)	53 ± 23 [#] (n=93)
Periostin in never-smokers (ng/mL)	60 ± 25 [#] (n=111)

Plus-minus values are means ± SD.

Mann-Whitney U-test for serum periostin levels between smokers and never-smokers shows no significant difference (p=0.091).