Serum Periostin: A Novel Biomarker for Asthma Management

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ABSTRACT
Chronic airway inflammation and remodeling are fundamental features of asthma. Even with adequate inhaled corticosteroid (ICS) treatment, there are still patients who exhibit Th2/eosinophilic inflammation and develop airflow limitation, a functional consequence of airway remodeling. There are few biomarkers that are applicable in the clinical setting that reflect refractory Th2/eosinophilic inflammation and remodeling of the asthmatic airways. Therefore, establishing such biomarkers is essential for managing patients who suffer from these conditions.

This review addresses the importance of serum periostin measurements by describing observations made in a KiHAC multicenter cohort with periostin used as a marker of pulmonary function decline and refractory Th2/eosinophilic inflammation in patients with asthma receiving long-term ICS treatment. Furthermore, serum periostin could be a companion diagnostic for targeted therapy against refractory Th2/eosinophilic inflammation. Finally, the distinct characteristics of serum periostin as compared to conventional biomarkers are addressed.

KEY WORDS
asthma, companion diagnostic, pulmonary function decline, refractory eosinophilia, serum periostin

INTRODUCTION
Airway inflammation and remodeling are fundamental features of asthma. To date, Th2/eosinophilic inflammation has been considered to be the dominant inflammatory pattern in asthma, although the involvement of Th1, Th17, and neutrophilic inflammation has been suggested based on recent evidence. With the introduction of inhaled corticosteroids (ICS) treatment, which efficiently reduces the production of Th2 and other cytokines by structural and inflammatory cells and induces inflammatory cell apoptosis, asthma in most patients can be successfully controlled. However, there still are patients with uncontrolled severe asthma, comprising 5%-10% of the total asthma population, and patients who develop airflow limitation, a functional consequence of airway remodeling, although these two populations often overlap.

With the advent of several methods to obtain samples from the airways, including induced sputum and exhaled air, we and others identified various biomarkers as being related to asthma pathophysiology. However, there are few biomarkers that can be easily accessed in clinical settings and may reflect refractory Th2/eosinophilic inflammation and remodeling of the asthmatic airways. Serum periostin may be one such biomarker to aid our understanding of the pathobiophysiology of asthma.

In this review, the impact of serum periostin measurements is addressed based on the axis of sustained Th2/eosinophilic inflammation and airflow remodeling in this ICS treatment era. Furthermore, the role of serum periostin as a companion diagnostic for currently available and forthcoming biologics is presented.

CANDIDATE MARKERS FOR Th2/EOSINOPHILIC INFLAMMATION AND REMODELING IN THE ASTHMATIC AIRWAY
Among a number of Th2 cytokines and mediators, interleukin (IL)-13 plays a pivotal role. This pleiot-
Periostin is a key molecule linking airway remodeling and Th2/eosinophilic inflammation

Matricellular protein is a recent concept that was coined for an extracellular matrix protein that causes a vicious cycle of inflammation and remodeling. Periostin is one of these matricellular proteins and is upregulated by IL-4 and IL-13 stimulation from airway epithelial cells and other structural cells. Taka-yama et al. were the first to demonstrate the deposition of periostin in the airway subepithelial layer in patients with asthma. Subsequently, in airway epithelial cells collected from patients with asthma, periostin was identified as one of the most upregulated genes by microarray assay, with a 4.4-fold increase as compared with healthy control subjects. This was confirmed in a recent study from the same research group by showing higher periostin gene expression in sputum cells from patients with asthma compared with sputum cells from healthy subjects.

Airway epithelial cells from children with asthma also had higher periostin expression (3.7-fold) than cells from atopic non-asthmatic or healthy children, which was not affected by ICS use. Furthermore, periostin expression in airway epithelial cells was correlated with airway basement membrane thickness (r = 0.56, p = 0.0002), and periostin could be detected in serum samples of patients with asthma, which largely reflected its level of production in the airways. This was possibly because periostin is secreted basally by airway epithelial cells in response to IL-13 stimulation and thus may easily leak into the airway capillaries.

Serum periostin has been identified as the single best predictor of airway eosinophilia in patients with severe asthma who remain symptomatic despite maximal ICS treatment (>1000 μg daily equivalent to fluticasone dipropionate; average %FEV1 60%, ACQ score 2.7) in the Bronchoscopic Exploratory Research Study of Biomarkers in Corticosteroid-refractory Asthma (BOBCAT). The superiority of serum periostin for predicting airway eosinophilia was shown by logistic regression analysis that included blood eosinophil counts, FeNO levels, and serum IgE levels (n = 59).

Taken together, periostin may be a key molecule that links remodeling and Th2/eosinophilic inflammation in the asthmatic airway. Therefore, its serum level could be a reliable marker of airway remodeling by reflecting refractory airway Th2/eosinophilic inflammation in patients receiving ICS treatment.

To assess this hypothesis, we determined the serum periostin levels in patients with asthma (n = 224; average age: 62.3 years; 171 females) who were recruited for the KIHAC multicenter study, a cohort to identify serum markers and genetic factors associated with pulmonary function decline in patients with asthma receiving long-term ICS treatment. In this study, annual changes in FEV1 were assessed from at least 1 year after initiating ICS treatment to the time of enrolment or later (average of 16.2 measurements for 8 years per individual). Serum periostin levels were measured using an enzyme-linked immunosorbent assay at Shino-test (Kanagawa, Japan), as previously described.

Serum periostin levels of patients with asthma (average: 92.8 ng/mL) were significantly higher than the pooled serum periostin levels (average: 39.1 ng/mL) of 66 healthy subjects (average age: 60.7 years; 40 males). Serum periostin levels showed weak but positive correlations with blood eosinophil counts, serum IgE and eosinophil cationic protein levels, ICS-un-treated periods, daily ICS maintenance doses at enrolment, and a history of admission due to asthma exacerbation (p < 0.05). The comorbidity of chronic sinusitis as assessed by a self-completed questionnaire was also a factor related to elevated serum periostin levels in this population (Fig. 1).

Among several serum markers that included serum eosinophil cationic protein, high sensitivity C reactive protein, IL-6, and IL-17, serum periostin levels were the sole biomarker for a greater annual decline in FEV1. When using dichotomous data for high (≥95 ng/mL; n = 85) and low (<95 ng/mL) serum periostin levels, which were determined by comparisons with healthy subjects, high serum periostin was associated with a decline in FEV1 of 30 mL·yr⁻¹ or greater inde-
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**Fig. 1** Associations between serum periostin levels and clinical indices, i.e. a) daily inhaled corticosteroids (ICS) maintenance dose, b) a history of admission due to asthma exacerbation, and c) comorbidity of chronic sinusitis. Values shown are means + SE.

![Graph a](image1.png)

**Fig. 2** Distributions of patients who underwent post-bronchodilator pulmonary function testing at study enrolment (n = 206) are shown based on patient age. Light blue bar indicates patients with post-bronchodilator FEV1/FVC of ≥0.7 (n = 136), yellow bar indicates patients with post-bronchodilator FEV1/FVC of <0.7 but with %predicted FEV1 of ≥80% (n = 35), and orange bar indicates patients with post-bronchodilator FEV1/FVC of <0.7 and with %predicted FEV1 of <80% (n = 35). The Berglund equation was used for predicted FEV1.

In this KiHAC population, post-bronchodilator pulmonary function results were obtained for 206 patients at enrolment when an average of eight years had passed since their first pulmonary function tests. A total of 70 (34%) fulfilled the criteria of fixed airflow limitation (post-bronchodilator FEV1/FVC of <0.7), and for patients aged ≥65 years (n = 103), 47% showed fixed airflow limitation; a substantial number of elderly patients with asthma (≤10 pack-years) had fixed airflow limitations (Fig. 2). In a cross-sectional analysis, high serum periostin was a factor associated with lower post-bronchodilator FEV1/FVC at enrolment for patients whose initial FEV1/FVC (pre-bronchodilator) was ≥0.7 and independent of the most intensive treatment step and ex-smoking (≤10 pack-years). We also found that one of the polymorphisms of the *POSTN* gene (rs3829365) that encodes for periostin was associated with higher serum periostin levels, suggesting that besides IL-13, a master regulator of periostin, the genetic background partly determines serum periostin levels, although replication studies are necessary to confirm this. Another *POSTN* gene polymorphism (rs9603226) was associated with a decline in FEV1 of ≥30 mL·yr⁻¹ by univariate analysis, particularly in conjunction with high serum periostin levels.
clusters. Thus, we propose that serum periostin should be measured for individuals who are characterized by these clusters. Of note, the late-onset, eosinophilic cluster in our population may overlap with the emerging cluster that was characterized by late-onset eosinophilic asthma with few symptoms for which serum periostin measurements may lead to better management of patients who are at risk of under-treatment with regard to pulmonary function when symptom-based strategies are implemented.

Because serum periostin may reflect latent airway inflammation, it is conceivable that serum periostin levels may predict the instability of asthma after ICS doses are tapered. In a pilot study, Kato et al. showed that initial serum periostin levels were higher in patients who were apparently well-controlled but showed deterioration in asthma at 12 weeks after the ICS dose was tapered compared with those who remained stable.

**SERUM PERIOSTIN AS A COMPANION DIAGNOSTIC FOR BIOLOGICS**

Several new biologics, including anti-IL-13 and anti-IL-5 antibodies, will be available in the very near future. Patients with uncontrolled asthma receiving ICS treatment are expected to benefit from these biologics; however, not all patients may respond to these costly biologics. Therefore, identifying responders to these biologics using good predictors (i.e., companion diagnostics) is necessary to efficiently apply these biologics.

In a phase IIb study of lebrikizumab (n = 219), an anti-IL-13 antibody, Corren et al. demonstrated that serum periostin was a good predictor of the response to lebrikizumab in patients with unstable asthma despite ICS therapy. The high serum periostin group (n = 110) showed an 8.2% increase in FEV1 in response to lebrikizumab compared with the placebo group, whereas there was a 1.6% increase in FEV1 for the serum low periostin group (n = 101).

Similarly, the EXTRA omalizumab study (total n = 850) showed that serum periostin could be a predictive marker of responses to omalizumab, anti-IgE antibody, in patients with severe asthma, in addition to blood eosinophil counts and FeNO levels. When patients had high serum periostin levels (n = 255), the rate of severe exacerbations declined by 30% when treated with omalizumab, whereas the decrease with omalizumab treatment was only 3% in the low serum periostin group (n = 279).

Periostin is overexpressed in the nasal tissues of patients with eosinophilic chronic rhinosinusitis (ECRS). We also determined serum periostin levels in patients with ECRS concomitant with severe asthma who were subsequently treated with omalizumab. These patients showed significant improvements in sinus CT scores as well as total and rhinological symptom scores in SNOT-20, scores for nasal congestion, and total nasal scores. These findings are consistent with those of the phase IIb study of lebrikizumab and the EXTRA omalizumab study.

**WHICH PATIENTS SHOULD BE MEASURED FOR SERUM PERIOSTIN?**

The aforementioned findings confirmed an association between periostin and airway remodeling, although these findings may be insufficient for extrapolation to clinical settings. We then translated our findings of serum periostin levels to patient-based information, by taking into account the time-axis.

Although Th2/eosinophilic inflammation is a dominant inflammatory pattern with asthma, complex interactions between genetic predisposition, environmental factors, and aging render asthma as a heterogeneous disease with varying phenotypes. To date, several attempts have been made to categorize the complex population of asthmatics into distinct subgroups using cluster analysis, an unbiased analysis. These studies have commonly identified benign asthma with little evidence of active disease, early-onset atopic asthma, and obese non-eosinophilic asthma.

Haldar et al. identified two additional clusters in refractory asthma: early-onset symptom-predominant asthma and late-onset eosinophilic asthma with few symptoms. The latter phenotype of late-onset eosinophilic asthma with few symptoms was also reported in a recent analysis of patients with adult-onset asthma. We also identified four distinct clusters in the KiHAC population. Among the four clusters identified, one cluster (n = 73) was characterized by late-onset, eosinophilic, and moderate decline in FEV1. Another cluster (n = 21) was characterized by mixed type inflammation (eosinophilic and neutrophilic) with the lowest FEV1, highest decline in FEV1, and lowest asthma control among the four clusters.

Serum periostin levels were the highest in the late-onset, eosinophilic cluster (n = 73), followed by the cluster with mixed type inflammation (n = 21). Most of the patients with a rapid FEV1 decline, defined as a decline of ≥30 mL·yr⁻¹, were included in these two clusters. Thus, we propose that serum periostin should be measured for individuals who are characterized by these clusters. Of note, the late-onset, eosinophilic cluster in our population may overlap with the emerging cluster that was characterized by late-onset eosinophilic asthma with few symptoms for which serum periostin measurements may lead to better management of patients who are at risk of under-treatment with regard to pulmonary function when symptom-based strategies are implemented.

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**Table 1 Multivariate analysis for the relationships between post-bronchodilator FEV1/FVC at enrolment and clinical indices in patients with asthma with initial FEV1/FVC of ≥0.7 (n = 142)**

<table>
<thead>
<tr>
<th></th>
<th>Correlation coefficients</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Step</td>
<td>-0.16</td>
<td>0.036</td>
</tr>
<tr>
<td>Smoking history</td>
<td>-0.03</td>
<td>ns</td>
</tr>
<tr>
<td>Serum periostin</td>
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<td>0.016</td>
</tr>
<tr>
<td>Blood neutrophil</td>
<td>-0.17</td>
<td>0.029</td>
</tr>
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</table>

Adjusted by sex, height, age at enrolment, and observation period from the first measurement.

1 According to the Global Initiative for Asthma 2010 guideline.

2 ≤10 pack-years.

3 high: ≥95 ng/mL, low: <95 ng/mL.
Fig. 3 Initial response levels of exhaled nitric oxide (FeNO) and serum periostin to inhaled corticosteroids treatment \((n = 37)\). Values shown are means ± SE.
*By paired t test, vs baseline.

Fig. 4 Schematic diagram of Th2/eosinophilic (Eo) airway pathobiology that could be evaluated by exhaled nitric oxide levels (FeNO) and serum periostin levels.

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**PERIOSTIN RESPONSES TO MEDICATIONS**

Th2/eosinophilic inflammation is not always steroid sensitive, which is often referred to as refractory inflammation in patients with severe asthma. This is also true for periostin production. From *in vitro* studies, steroid treatment efficiently decreases IL-4/IL-13-induced periostin production by airway epithelial cells\(^{35}\) and fibroblasts\(^{34}\) but does not inhibit TGF-β-induced periostin production by fibroblasts or IL-4/IL-13-induced periostin production by microvascular endothelial cells\(^{55}\). Serum periostin levels were significantly decreased by an average of 17.2% (placebo corrected) from the baseline levels after 14 days of treatment with oral prednisolone (0.5 mg/kg/day) in the BIOAIR study \((n = 118)\).\(^{56}\) A 12-week treatment with lebrikizumab also decreased serum periostin levels by 9.7% (placebo corrected) in all patients and by 14.4% in the high periostin group.\(^{57}\) In steroid-naïve patients with asthma, introduction of ICS (equivalent to fluticasone propionate 400 μg daily) significantly decreased serum periostin levels at 24 weeks but only by 5.4% from the baseline \((n = 37;\) mean age 55 years, 10 males) (Fig. 3) (Otsuka K, Takeda T, et al. unpublished data).

Potent systemic anti-inflammatory treatments may decrease serum periostin levels, whereas the effects of ICS on serum periostin levels appear to be minimal. This was in contrast to the changes in FeNO levels that significantly decreased by 27.4% at 12 weeks from the baseline levels in the same steroid naïve patients \((n = 37)\) (Fig. 4). Further studies will be needed...
to confirm these preliminary findings, although FeNO levels may reflect relatively acute inflammation in the Th2/eosinophilic airways, whereas serum periostin levels may reflect chronic or latent inflammation and remodeling of the asthmatic airways with ICS treatment (Fig. 4).

Blood eosinophil counts, FeNO, and serum periostin levels may be compensatory or composite markers of Th2/eosinophilic inflammation, although serum periostin levels may be distinct from other conventional biomarkers by integrating the information for chronic inflammation and remodeling in the Th2/eosinophilic airway. Furthermore, as different from FeNO and blood eosinophil counts, serum periostin levels are stable and with little variability, which is required for a reliable biomarker. In the phase IIb study of lebrikizumab, the average coefficients of variation (CV) for FeNO, blood eosinophil counts, and serum periostin that were assessed at 1 week apart during the run-in period were 19.8%, 21.3%, and 5.0%, respectively. Consistently, in the BOBCAT study, CV for FeNO and serum periostin that were assessed at 2-3 weeks apart were 8.2% and 2.2%, respectively.

CONCLUSION

Although more studies are needed to validate and establish its utility in asthma management, serum periostin is a novel biomarker in asthma that integrates the information on refractory Th2/eosinophilic inflammation and remodeling of the airways and could be a companion diagnostic for Th2-targeted therapy. This distinct characteristic of serum periostin may provide a platform for elucidating the mechanisms underlying persistent airway Th2/eosinophilic inflammation in asthma during this ICS treatment era.

ACKNOWLEDGEMENTS

The author is immensely grateful to Drs Kenji Izuhiara (Saga Medical School), Shoichiro Ohta (Saga Medical School), and Junya Ono (Shino-Test) for the measurement of serum periostin levels and fruitful discussion on periostin; Organizers and collaborators of the Kinki Hokuriku Airway disease Conference (KiHAC), Drs Yuji Tohda (Kinki University), Hideo Kita (Takatsuki Red Cross Hospital), Takahiko Horiguchi (Fujita Health University Second Educational Hospital), Kazunobu Kuwabara (Fujita Health University Second Educational Hospital), Keisuke Tomii (Kobe City Medical Center General Hospital), Kojiro Otsuka (Kobe City Medical Center General Hospital), Masaki Fujimura (Kanazawa University), Noriyuki Ohkura (Kanazawa University), Katsuyuki Tomita (Kinki University), Akihito Yokoyama (Kochi University), Hiroshi Ohnishi (Kochi University), Yasutaka Nakano (Shiga University of Medical Science), Tetsuya Oguma (Shiga University of Medical Science), Soichiro Hozawa (Hiroshima Allergy and Respiratory Clinic), Isao Ito*, Tsuyoshi Oguma*, Hideki Inoue*, Toshiyuki Iwata*, Yumi Izuhiara*, and Akio Niimi* for the fruitful discussion on the project of KiHAC multicenter cohort and data collection; Drs Mayumi Tamari (RIKEN), Tomomitsu Hirota (RIKEN), and Tetsuji Yokoyama (National Institute of Public Health) for the thoughtful comments on genetic and statistical analysis; Drs Yoshihiro Kanemitsu*, Tadao Nagasaki*, and Tomoko Tajiri* for their contribution to lung function study, cluster analysis, and omalizumab ECRS study, respectively; Dr Michiaki Mishima* for his general guidance and constant support. (*, Kyoto University.)

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