Factors Contributing to an Accelerated Decline in Pulmonary Function in Asthma

Yoshihiro Kanemitsu¹, Hisako Matsumoto¹, Michiaki Mishima¹ and the KiHAC Respiratory Medicine Group

ABSTRACT

Patients with asthma show a steeper age-related decline in pulmonary function than healthy subjects, which is often alleviated after the initiation of treatment with inhaled corticosteroids (ICS). However, there still are patients who develop irreversible airflow limitations despite receiving adequate ICS treatment. The identification of the characteristics of such patients and biomarkers of progression for airflow limitation, a functional consequence of airway remodeling, is considered important in the management of asthma.

A variety of biomarkers are associated with the forced expiratory volume in 1 s (FEV₁) in asthma in a cross-sectional fashion. However, few biomarkers are known to reflect the decline in pulmonary function, particularly in patients with asthma who receive ICS treatment. Recently periostin, a matricellular protein that prolongs Th2/eosinophilic inflammation and reflects airway remodeling, was reported to be detected in serum. In a Kinki Hokuriku Airway disease Conference multicenter cohort study, we demonstrated that among several serum markers, high serum periostin level, particularly ≥95 ng/mL, was the only marker associated with a greater annual decline in FEV₁ and a decline in FEV₁ of ≥30 mL·yr⁻¹. A variant (rs9603226) of the POSTN gene that encodes periostin was also involved in the frequency of a decline in FEV₁ of ≥30 mL·yr⁻¹.

Our results suggest that the serum periostin level is a useful marker reflecting pulmonary function decline in patients with asthma receiving ICS.

KEY WORDS
asthma, biomarker, inhaled corticosteroids, periostin, pulmonary function decline

INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways characterized by the infiltration of various inflammatory cells, cytokines, and mediators, all of which contribute to the development of airway hyperresponsiveness (AHR), remodeling,¹ and the progression of airflow limitation,² a functional consequence of airway remodeling. As a result of inhaled corticosteroids (ICS), the mainstay of asthma treatment, airway inflammation³ and AHR³ have been well controlled, which then prevents the progression of irreversible airflow limitations.⁴⁻⁷ However, some patients with asthma still develop fixed airflow limitations despite intensive treatment. Indeed, short-term treatment with ICS has been shown to significantly decrease airway wall thickening on computed tomography,⁸ whereas long-term treatment with ICS may not consistently reverse the changes in the remodeled airways.⁹ These findings suggest that the response to long-term treatment with ICS may be heterogeneous among asthmatic patients, which may relate to insensitivity to ICS. Clarifying the background of asthmatics with progressive airflow limitation would be important by itself¹⁰ and also for providing clues about ways to overcome insensitivity to ICS treatment.

¹Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan.
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Correspondence: Hisako Matsumoto, MD, PhD, Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, 54 Kawahara-cho, Shogoin, Sakyō-ku, Kyoto 606-8507, Japan.
Email: hmatsumo@kuhp.kyoto-u.ac.jp
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Our study group and others have demonstrated a variety of biomarkers useful in the understanding of asthma pathogenesis.\textsuperscript{11-23} Those include markers in the sputum supernatant,\textsuperscript{11-19} exhaled air,\textsuperscript{20,21} and blood.\textsuperscript{22,23} However, there have been a limited number of biomarkers that could be applicable in actual clinical settings, as mentioned in the recent statement from the National Institutes of Health.\textsuperscript{24} The development of such clinically applicable biomarkers is thus warranted for better asthma management.

In this review article, we summarize the factors that are associated with a decline in pulmonary function. The effects of ICS treatment are also presented. We show the role of the serum periostin level as a biomarker that reflects refractory Th2/eosinophilic inflammation and pulmonary function decline in patients with asthma who receive ICS.

**RISK FACTORS OF PULMONARY FUNCTION DECLINE**

Pulmonary function reaches a maximum in the early twenties and starts to decline from around the age 25.\textsuperscript{25} The earlier studies on the contributing factors for a decline in pulmonary function demonstrated that the recent onset of asthma, frequent asthma symptoms and severe exacerbations, AHR, and smoking history could be risk factors for the decline. Blood and sputum eosinophilia and genetic predisposition also influenced the accelerated decline in pulmonary function in patients with asthma (Table 1). In the following paragraphs, details on these contributing factors are described. It should be noted, however, that few of the studies addressed whether studied patients had been consistently treated with ICS during the observation periods.

**RECENT ONSET OF ASTHMA AND LONG-STANDING ASThma**

The recent onset of asthma appears to have a negative impact on pulmonary function. A 5-year follow-up survey of the Copenhagen City Heart Study\textsuperscript{26} and another longitudinal study\textsuperscript{27} both revealed that adults who newly developed asthma showed an accelerated decline in FEV\textsubscript{1}, whereas those who had been diagnosed as having asthma showed a similar degree of decline in FEV\textsubscript{1} to that of nonasthmatic subjects\textsuperscript{26,27}. A subsequent study showed that patients with disease duration of <15 years showed a steeper decline in FEV\textsubscript{1} than those with a longer disease duration.\textsuperscript{28} In this analysis, baseline FEV\textsubscript{1} was unrelated to disease duration.\textsuperscript{28}

On the other hand, long-standing asthma is also an important factor for the development of airflow limitation in patients with asthma, particularly in patients with severe asthma receiving maximal treatment, including systemic corticosteroids. The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens study (TENOR study) showed that 60% of people with severe or difficult-to-treat asthma had persistent airflow limitation as defined by post-bronchodilator FEV\textsubscript{1}/FVC of \(\leq 0.7\) at two consecutive annual visits. This study also revealed that longer disease duration was one of the risk factors that was associated with persistent airflow limitation.\textsuperscript{29} Another cross-sectional study that compared younger patients and elderly patients with early-onset or late-onset asthma found that elderly patients who had early-onset asthma had the most severe airway obstruction.\textsuperscript{30} These findings suggest that long-standing asthma may be also involved in a progressive loss of pulmonary function.\textsuperscript{29,30}

**SEVERITY OF ASTHMA**

AHR, one of the hallmarks of asthma, is associated with not only asthma symptoms, such as wheezing\textsuperscript{31} and dyspnea,\textsuperscript{32} but also impaired pulmonary function growth\textsuperscript{33} and pulmonary function decline.\textsuperscript{34,35} In an 18-year follow-up study, Peat et al. demonstrated that AHR to histamine measured at the end of their study period was associated with accelerated annual decline in FEV\textsubscript{1} in patients with asthma.\textsuperscript{34} A subsequent study revealed that AHR had a marked influence on the annual decline in FEV\textsubscript{1} in atopic patients but not in nonatopic patients.\textsuperscript{35} An epidemiological study of a Dutch cohort revealed that AHR was independently associated with an accelerated decline in FEV\textsubscript{1}, irrespective of gender, smoking status, age, respiratory symptoms, and baseline FEV\textsubscript{1} levels.\textsuperscript{36}

In addition, persistent symptoms may be a predictive factor for irreversible airflow limitation and accelerated pulmonary function decline in patients with severe asthma refractory to corticosteroid therapy. Among the many symptoms of asthma such as sputum production, cough, wheezing, and dyspnea, an association has been reported between chronic mucous hypersecretion and an accelerated decline in FEV\textsubscript{1} in nonsmoking patients with asthma.\textsuperscript{2,26,37}

Initial increased airway reversibility to short-acting \(\beta_2\) agonists and long-term treatment with oral corticosteroids were also risk factors for the development of irreversible airflow obstruction.\textsuperscript{38} A 10-year follow-up survey was conducted to evaluate the frequency of irreversible airflow obstruction in life-long nonsmoking adults with long-standing moderate to severe asthma; the mean age was 37 years, mean disease duration at enrollment was 16 years, and 72% patients took ICS. At the end of the study, 23% of the studied patients fulfilled the criteria for irreversible airflow obstruction and showed a greater decline in FEV\textsubscript{1} than patients with reversible airflow obstruction.\textsuperscript{38}

Two recent studies, a historical cohort\textsuperscript{39} and a prospective cohort,\textsuperscript{40} showed that severe asthma exacerbation may result in an accelerated loss of pulmonary function. In patients with moderate to severe asthma who underwent a 11-year follow-up, those who frequently experienced asthma exacerbations (-0.10 ex-
Recent onset of asthma/long-standing asthma

- Ulrik et al. 1994
- Burrows et al. 1991
- Cibella et al. 2002

Severity of asthma/symptoms

- Peat et al. 1987
- van Schayck et al. 1991
- Lange et al. 1998
- Postma et al. 1995
- Bai et al. 2007
- O’Byrne et al. 2009
- Apostol et al. 2002
- James et al. 2005
- Broekema et al. 2010

Smoking

- van Veen et al. 2008
- van Rensen et al. 2005
- Pasternack et al. 2005
- Kanemitsu et al. 2013

Inflammation

- Jongepier et al. 2004
- Dijkstra et al. 2006
- Barton et al. 2009

Genetic predisposition

- Genetic predisposition

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Subsequently, the Coronary Artery Risk Development In Young Adults study of subjects with the average age of 24.8 at baseline showed that the initiation of smoking or exposure to it before age 15 was associated with a rapid decline in FEV1 compared with those participants who never smoked or started smoking later. Furthermore, the combination of asthma and heavy smoking (≥15 cigarettes per day) had a synergic effect on the rate of decline in FEV1. In the Busselton Health Survey conducted by James et al., where the average baseline age of the participants was 40, showed that asthma and smoking additively contributed to an accelerated decline in FEV1. Lastly, Perret et al. showed a synergic interaction be-

SMOKING

Active smoking worsens not only asthma-related symptoms but also airway inflammation but also accelerates a decline in pulmonary function in patients with asthma, either in synergistic or additive ways. In the Copenhagen City Heart study, smokers who had asthma had a steeper decline in FEV1 than nonsmokers with asthma in a 15-year follow-up.
between asthma and active smoking on the development of fixed airway obstruction (post bronchodilator FEV1/FVC of <0.7),44 which was only observed in atopic patients with asthma.

INFLAMMATION
Asthma is classically characterized by Th2 and eosinophilic inflammation. Several cross-sectional studies showed that sputum eosinophilia and increased eosinophil cationic protein levels were independent risk factors for persistent airflow limitation in patients with severe refractory asthma.16,17 In a longitudinal study of steroid-naïve patients with asthma, during a mean of 9-year follow-up, Broekema et al. demonstrated that a greater annual decline in FEV1 was associated with a high number of eosinophil in the sputum or high eosinophil cationic protein levels, particularly when patients showed a decline in FEV1 of ≥30 mL·yr⁻¹.18 Ulrik also proposed the possibility that higher blood eosinophil counts in childhood asthma were associated with lower predicted FEV1 in early adulthood in patients with asthma.45 In patients with difficult-to-treat asthma, van Veen found that exhaled nitric oxide of ≥20 parts per billion was a predictor of accelerated decline in FEV1 if their baseline predicted FEV1 was ≥80%.21

Apart from eosinophils, neutrophils and lymphocytes may also be involved in impaired pulmonary function.19,46 Shaw et al., in a cross-sectional study, showed that increased sputum neutrophil counts were associated with lower %FEV1.19 Thereafter, we found negative correlation between pulmonary function and the sputum levels of YKL-40 that was mostly expressed in sputum neutrophils and macrophages.13 In one study with 7.5-year follow-up, CD8⁺ T lymphocytes in bronchial tissue were solely related to an accelerated decline in FEV1.46 In nonatopic patients with asthma, chronic infection with Chlamydia pneumonias was considered a risk factor for an accelerated decline in FEV1.47

**GENETIC PREDISPOSITION**
The etiology of asthma is complicated because of its heterogeneity which originates in genetic and environmental interaction and variability. Positional cloning, candidate gene screenings, and genome-wide association (GWA) studies have identified relationships between gene variants (single-nucleotide polymorphisms; SNPs) and susceptibility to asthma. A recent GWA study did not identify any SNPs that contributed to the decline of pulmonary function in adults with asthma.48 However, earlier candidate gene screenings that were conducted in a mostly Caucasian population showed associations between pulmonary function decline and several gene variants [SNPs of A disintegrin and metalloproteinase domain 33 (ADAM33)49, estrogen receptor α (ESR1)50 and plasminogen activator receptor (PLAUR)51] (Table 1, 2). These associations have been well summarized elsewhere.52 In a recent cross-sectional study, SNPs of four genes that are involved in the Th1 or IL-12 cytokine family pathways (IL12A, IL12RB1, STAT4, and IRF2) were associated with lower percent predicted FEV1 and disease severity of asthma.53 The authors proposed a hypothesis of “two-step progression asthma genetic model,” where genes variants in the Th2 pathways confer asthma susceptibility and then variants in the Th1 or IL-12 cytokine family pathways affect the impaired pulmonary function.53

**THE EFFECT OF ICS ON THE DECLINE IN PULMONARY FUNCTION**
There is increasing evidence that long-term use of ICS yields beneficial effects on the decline in pulmonary function.47,55 In the Inhaled Steroids Treatment As Regular Therapy in Early Asthma study, long-term...
treatment with ICS for ≥3 years decreases the frequency of severe exacerbations, and improves asthma control, and prevents the progression of the decline in FEV₁. Meanwhile, several studies have indicated that the efficacy of ICS may vary according to gender, smoking habits, or serum total IgE levels. Collectively, serum periostin may reflect Th2/ eosinophilic inflammation and airway remodeling in asthma.

In a multicenter cohort study of Kinki Hokuriku Airway disease Conference (KIHAC), we evaluated the factors associated with an accelerated decline in pulmonary function in 224 asthmatics receiving ICS treatment (average age 62.3 years, 171 females). In this study, we assessed the annual changes in FEV₁ from at least 1 year after the initiation of ICS treatment to the time of enrollment or later (average, 16.2 measurements over 8 years per individual). Blood granulocyte counts and several serum markers, including serum periostin, high-sensitivity C-reactive protein, and eosinophil cationic protein were examined in association with annual decline in FEV₁. Serum periostin levels were measured using an enzyme-linked immunosorbent assay at Shino-test (Kanagawa, Japan). After the adjustment for several confounding factors, high serum periostin levels, particularly if they were ≥95 ng/mL, were solely associated with a greater annual decline in FEV₁. This level was determined using the receiver operating characteristic curve analysis with the highest specificity (0.985) from a comparison between 224 patients with asthma (average 92.8 ng/mL) and 66 healthy subjects (average 39.1 ng/mL). Serum periostin levels were positively correlated with the peripheral blood eosinophil counts (r = 0.30, p = 0.0001), serum eosinophil cationic protein levels (r = 0.25, p = 0.0005), and serum total IgE levels (r = 0.29, p = 0.0001). Other independent risk factors for the decline in FEV₁ of ≥30 mL·yr⁻¹, i.e., the most intensive treatment step and a history of smoking with light smoking (≤10 pack-years) were consistent with previ-

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**Contributing Factors of Lung Function**

**SERUM PERIOSTIN, A PROMISING BIO-MARKER OF PULMONARY FUNCTION DECLINE**

Dozens of biomarkers are associated with FEV₁ in a cross-sectional fashion. However, few biomarkers that reflect pulmonary function decline have been identified. Periostin is a matricellular protein, secreted from airway epithelial cells and lung fibroblasts in response to IL-4 and IL-13 signaling. It can bind to other extracellular matrix components such as collagens I, III, and V, fibronectin, tenascin-C, and periostin itself. Periostin gene expression in airway epithelial cells of patients with asthma was upregulated compared with that in healthy subjects and its levels correlated with the reticular basement membrane thickness. A postmortem study demonstrated the deposition of periostin on the subepithelial layer of asthmatic airways. Serum periostin was recently identified as the best biomarker to reflect persistent airway eosinophilia in patients with severe asthma who were receiving high-dose ICS (≥1000 µg/day) and also predicted the response to anti-IL-13 antibody treatment. Collectively, serum periostin may reflect Th2/eosinophilic inflammation and airway remodeling in asthma.

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**Fig. 1** Relationship between the serum periostin level and the annual decline in FEV₁.

**Fig. 2** Patients who showed a decline in FEV₁ of ≥30 mL·yr⁻¹ were considered rapid decliners.
ous findings,2,25,43

On univariate analysis, supplemental findings of the KiHAC cohort study identified risk factors for a greater decline in FEV\(_1\) such as incomplete adherence to medications,62 lower Asthma control test\(^\circ\) scores,63 and comorbidity with or history of sinusitis\(^4\) and diabetes mellitus.65 These findings are also in agreement with previous studies: (1) Shirai et al. demonstrated weak associations between a low Asthma control test\(^\circ\) score and impaired pulmonary function (low \%FEV\(_1\) and \%PEF),63 (2) chronic sinusitis, one of the common comorbidities of asthma, is related to frequent asthma exacerbations66 and decline in pulmonary function,64 and (3) patients with type 2 diabetes mellitus with poor glycemic control is associated with the impaired pulmonary function.65

Lastly, a polymorphism of the \text{POSTN} gene, which encodes periostin, was also associated with an accelerated decline in pulmonary function in univariate analysis.60 Patients with the AA/AG genotypes of rs9603226 that is located at intron 21 showed a higher frequency of a decline in \(\geq 30\) mL than those with the GG genotype (30\% vs 16\%) \(p = 0.02\). In patients who had high serum periostin levels (\(\geq 295\ ng/mL\)), the frequency of rapid decliners was greater in patients with of the AA/AG genotypes of rs9603226 than in those with the GG genotype (45\% vs 19\%) \(p = 0.01\) (Table 2, Fig. 2).

CONCLUSION

Even in patients receiving long-term ICS treatment, a history of smoking, albeit with a light smoking history, and the most intensive treatment step remained characteristics of the rapid decliners, which was in line with the findings of the earlier studies. Independent from these clinical characteristics, high serum periostin, a marker of refractory Th2/eosinophilic inflammation, was identified as a novel biomarker reflecting an accelerated decline in FEV\(_1\) in patients with asthma receiving ICS treatment. Targeting refractory Th2/eosinophilic inflammation using serum periostin might yield better outcomes in asthma management.

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