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REVIEW ARTICLE

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Factors Contributing to an Accelerated Decline in Pulmonary Function in Asthma

Yoshihiro Kanemitsu[1], Hisako Matsumoto[1], Michiaki Mishima[1] 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 (FEV_1) 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 FEV_1 and a decline in FEV_1 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 FEV_1 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 inflammation[3] and AHR[3] 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 itself[10] and also for providing clues about ways to overcome insensitivity to ICS treatment.

[1]Department 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, Sakyo-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.[11-23] Those include markers in the sputum supernatant,[11-19] exhaled air,[20,21] and blood.[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.[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.[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[26] and another longitudinal study[27] both revealed that adults who newly developed asthma showed an accelerated decline in FEV_1, whereas those who had already been diagnosed as having asthma showed a similar degree of decline in FEV_1 to that of nonasthmatic subjects[26,27]. A subsequent study showed that patients with disease duration of <15 years showed a steeper decline in FEV_1 than those with a longer disease duration.[28] In this analysis, baseline FEV_1 was unrelated to disease duration.[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_1/FVC of ≤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.[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.[30] These findings suggest that long-standing asthma may be also involved in a progressive loss of pulmonary function.[29,30]

SEVERITY OF ASTHMA

AHR, one of the hallmarks of asthma, is associated with not only asthma symptoms, such as wheezing[31] and dyspnea,[32] but also impaired pulmonary function growth[33] and pulmonary function decline.[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_1 in patients with asthma.[34] A subsequent study revealed that AHR had a marked influence on the annual decline in FEV_1 in atopic patients but not in nonatopic patients.[35] An epidemiological study of a Dutch cohort revealed that AHR was independently associated with an accelerated decline in FEV_1, irrespective of gender, smoking status, age, respiratory symptoms, and baseline FEV_1 levels.[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 mucus hypersecretion and an accelerated decline in FEV_1 in nonsmoking patients with asthma.[2,26,37]

Initial increased airway reversibility to short-acting β_2 agonists and long-term treatment with oral corticosteroids were also risk factors for the development of irreversible airflow obstruction.[38] A 10-year follow-up survey was conducted to evaluate the frequency of irreversible airway 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_1 than patients with reversible airflow obstruction.[38]

Two recent studies, a historical cohort[39] and a prospective cohort,[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-

Table 1 Risk factors for pulmonary function decline in patients with asthma

Major risk factors	Authors, Published year	Follow-up period (years)	*n* (asthma)	Disease duration (years)	Measurements of FEV_1 (per individual)	Specific factors associated with pulmonary function decline in FEV_1
Recent onset of asthma/ long-standing asthma	Ulrik *et al.* 1994[26]	5	10952 (396)	Data not shown	2	Age at disease onset (>20 years), Chronic mucus secretion
	Burrows *et al.* 1991[27]	13.1	1185 (40)	9.3	7.4	Age at disease onset (>60 years)
	Cibella *et al.* 2002[28]	5	142 (142)	5.5 (males), 8.8 (females)	10	Disease duration (<15 years), Reversibility (≥15%), Young males
Severity of asthma/ symptoms	Peat *et al.* 1987[34]	18	278 (92)	Data not shown	4-7	Airway hyperresponsiveness
	van Schayck *et al.* 1991[35]	2	71 (71)	Data not shown	6	Airway hyperresponsiveness in atopic patients
	Lange *et al.* 1998[2]	15	17506 (1095)	Data not shown	3	Chronic mucus secretion, Smoking
	Postma *et al.* 1995[37]	13	1439 (231)	Data not shown	Maximal 8	Chronic mucus secretion, Reversibility (≥25%)
	Bai *et al.* 2007[39]	11	93 (93)	Data not shown	20.8	Severe exacerbation
	O'Byrne *et al.* 2009[40]	3	315 (315)	0-2	14	Severe exacerbation
Smoking	Apostol *et al.* 2002[25]	10	5057 (613)	Data not shown	4	Smoking
	James *et al.* 2005[43]	29	9317 (1301)	Data not shown	Maximal 7	Smoking
Inflammation	Broekema *et al.* 2010[18]	5-14	47 (47)	Data not shown	2	Sputum eosinophils, Sputum eosinophil cationic protein
	van Veen *et al.* 2008[†21]	5.7	98 (98)	18.5	2	Exhaled nitric oxide
	van Rensen *et al.* 2005[46]	7.5	32 (32)	Data not shown	2	Bronchial infiltrate of CD8 T lymphocyte
	Pasternack *et al.* 2005[47]	15	245 (83)	15	2	Chronic *Chamydophila pneumoniae* infection in nonatopic asthmatics
	Kanemitsu *et al.* 2013[†60]	8	224 (224)	20.2	16.2	Serum periostin, genetic predisposition (*POSTN*), Treatment Step 5, ex-smoking (≤10 pack-years)
Genetic predisposition	Jongepier *et al.* 2004[49]	22	152 (152)	Data not shown	29	Genetic predisposition (*ADAM33*)
	Dijkstra *et al.* 2006[50]	20.1	129 (129)	Data not shown	23 (males) 20 (females)	Genetic predisposition (*ESR1*)
	Barton *et al.* 2009[51]	20.4	2819 (124)	Data not shown	22.5	Genetic predisposition (*PLAUR*)

[†] All participants took ICS treatment.

acerbations·yr^{-1}) showed greater annual decline in FEV_1 than those with infrequent exacerbations.[39] Meanwhile, ICS treatment may repress the frequency of severe exacerbations and the decline in FEV_1 in patients with mild persistent asthma.[40]

SMOKING

Active smoking worsens not only asthma-related symptoms[41] and airway inflammation[14,42] but also accelerates a decline in pulmonary function in patients with asthma,[2,25,43] either in synergistic[25] or additive ways.[43] In the Copenhagen City Heart study, smokers who had asthma had a steeper decline in FEV_1 than nonsmokers with asthma in a 15-year follow-up.[2] 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 FEV_1 compared with those participants who never smoked or started smoking later.[25] Furthermore, the combination of asthma and heavy smoking (≥15 cigarettes per day) had a synergic effect on the rate of decline in FEV_1.[25] 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 FEV_1.[43] Lastly, Perret *et al.* showed a synergic interaction be-

Table 2 Effects of polymorphisms on an accelerated decline in FEV_1 in patients with asthma

Authors, Published year	Gene	SNP No.	Location	Allelic	Risk genotype	Decline in FEV_1 ($mL \cdot yr^{-1}$)	Difference compared with major homozygous genotypes ($mL \cdot yr^{-1}$)
Jongepier *et al.* 2004[49]	*ADAM33*	rs528557	3'UTR	G/C-	CC	data not shown	-23.7
Dijkstra *et al.* 2006[50]	*ESR1*	rs2077647	Exon1	C/T	TC	-23.1	-11.6
					CC	-27.2	-15.7
		rs9340799	Intron1	G/A	AA	-27.6	-16.1
		rs2234693	Intron1	C/T	TT	-29.2	-13.3
		rs9322331	Intron1	T/C	CC	-25.8	-15.2
		rs4870056	Intron1	A/G	GG	-28.4	-13.0
Barton *et al.* 2009[51]	*PLAUR*	rs2356338	5'UTR	G/T	TT	-34.4	-14.6
		rs4251953	3'UTR/Intron	G/A	GA/GG	-37.9	-15.9
		rs4802189	3'UTR	C/A	CA/AA	-32.4	-13.4
		rs4803648	3'UTR	T/A	AA	-36.1	-17.0
					TA/AA	-31.0	-10.8
Kanemitsu *et al.* 2013[60]	*POSTN*	rs9603226	Intron21	G/A	GA/AA	-11.4	-7.3

tween asthma and active smoking on the development of fixed airway obstruction (post bronchodilator FEV_1/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 FEV_1 was associated with a high number of eosinophil in the sputum or high eosinophil cationic protein levels, particularly when patients showed a decline in FEV_1 of ≥30 $ml \cdot yr^{-1}$.[18] Ulrik also proposed the possibility that higher blood eosinophil counts in childhood asthma were associated with lower predicted FEV_1 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 FEV_1 if their baseline predicted FEV_1 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 $\%FEV_1$.[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 FEV_1.[46] In nonatopic patients with asthma, chronic infection with *Chlamydophila pneumoniae* was considered a risk factor for an accelerated decline in FEV_1.[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 FEV_1 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.[4-7] In the Inhaled Steroids Treatment As Regular Therapy in Early Asthma study, long-term

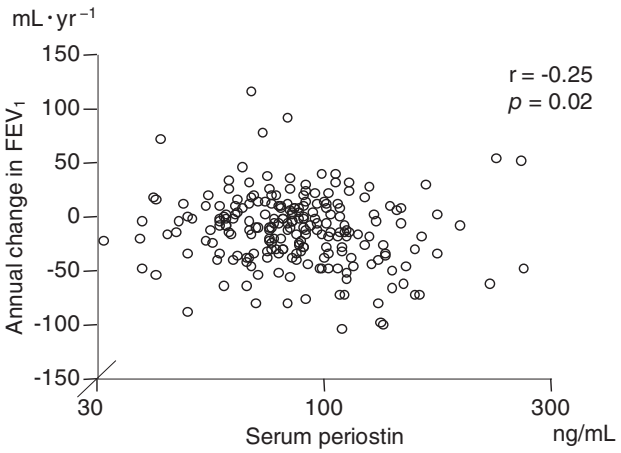

Fig. 1 Relationship between the serum periostin level and the annual decline in FEV_1.

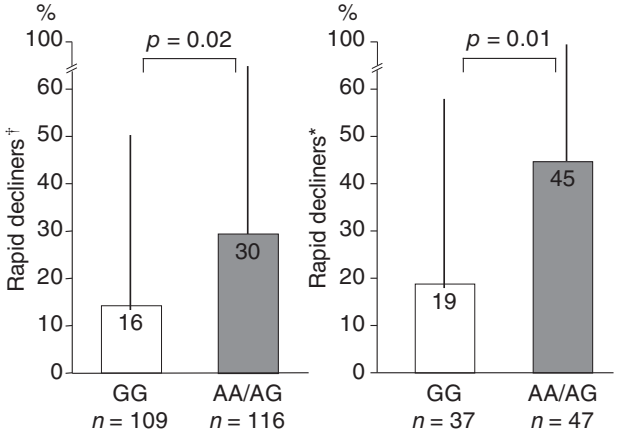

Fig. 2 †Patients who showed a decline in FEV_1 of ≥30 mL·yr^{-1} were considered rapid decliners.

treatment with ICS for ≥3 years decreases the frequency of severe exacerbations,[40,54] improves asthma control,[54] and prevents the progression of the decline in FEV_1.[4] Meanwhile, several studies have indicated that the efficacy of ICS may vary according to gender,[5] smoking habits,[5] or serum total IgE levels.[6] Dijkstra *et al.* demonstrated that only male patients who had smoked <5 pack-years benefited from intervention with ICS treatment, showing an attenuated FEV_1 decline during a median follow-up of 23 years (-54.4 mL·yr^{-1} before ICS intervention *vs* -17.7 mL·yr^{-1} after ICS intervention).[5] In the European Community Respiratory Health Survey study, with a median follow-up of 9 years, patients with increased serum total IgE levels (>100 kU/L) who had been treated with ICS for ≥4 years showed less decline in FEV_1 than those who did not receive ICS treatment (10.7 mL·yr^{-1} lower decline than ICS nonusers).[6] This beneficial effect of ICS was not observed in patients with lower serum total IgE levels.[6]

SERUM PERIOSTIN, A PROMISING BIOMARKER OF PULMONARY FUNCTION DECLINE

Dozens of biomarkers are associated with FEV_1 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[55] and lung fibroblasts[56] 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.[56] Periostin gene expression in airway epithelial cells of patients with asthma was upregulated compared with that in healthy subjects[57] and its levels correlated with the reticular basement membrane thickness.[55] A postmortem study demonstrated the deposition of periostin on the subepithelial layer of asthmatic airways.[56] 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)[58] and also predicted the response to anti-IL-13 antibody treatment.[59] 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).[60] In this study, we assessed the annual changes in FEV_1 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 FEV_1. Serum periostin levels were measured using an enzyme-linked immunosorbent assay at Shino-test (Kanagawa, Japan).[61] 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 FEV_1 (Fig. 1). 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 FEV_1 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-

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® scores,[63] and comorbidity with or history of sinusitis[64] 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® 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 exacerbations[66] 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 *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 ≥30 mL than those with the GG genotype (30% *vs* 16%) ($p = 0.02$). In patients who had high serum periostin levels (≥95 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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