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Increased Serum Periostin Levels and Eosinophils in Nasal Polyps Are Associated with the Preventive Effect of Endoscopic Sinus Surgery for Asthma Exacerbations in Chronic Rhinosinusitis Patients

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Keywords
Chronic rhinosinusitis · Asthma · Serum periostin · Eosinophilic nasal polyp · Endoscopic sinus surgery

Abstract
Background: Eosinophilic nasal polyps (NPs) are associated with the presence of asthma in chronic rhinosinusitis (CRS) patients. Serum periostin has been considered a relevant biomarker for unified airway diseases. ***Objective:*** To determine the utility of biomarkers including serum periostin that reflects reduction of exacerbations of comorbid asthma in CRS patients. ***Methods:*** We prospectively recruited 56 CRS patients who were subjected to undergo endoscopic sinus surgery (ESS) (20 with asthma) between October 2015 and December 2017 and followed them for 1 year after ESS. Blood eosinophil count, serum periostin, and fractional nitric oxide (FeNO) were measured at enrollment. How these type 2-driven biomarkers reflect comorbid asthma was determined using receiver operating characteristic (ROC) analysis. The frequency of asthma exacerbations during 1 year was counted both before and after ESS. Associations between preoperative biomarkers including eosinophils in NPs and asthma exacerbations were evaluated. ***Results:*** Blood eosinophil count, FeNO, and serum periostin levels were significantly higher in CRS patients with asthma than in those with-

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out ($p < 0.01$ for all) and discriminated comorbid asthma among CRS patients ($p < 0.05$; AUC > 0.80 for all). The increased preoperative serum periostin correlated with lower absolute number of postoperative exacerbations ($\rho = -0.49$, $p = 0.03$) and its relative reduction after ESS ($\rho = 0.53$, $p = 0.03$) in asthmatic patients. Increased eosinophils in NPs were also associated with reduced asthma exacerbations. ***Conclusion:*** Preoperative increased serum periostin and eosinophils in NPs are associated with the preventive effect of ESS for asthma exacerbations in CRS patients comorbid with asthma.

Introduction

Both asthma and chronic rhinosinusitis (CRS) are significant problems worldwide in terms of not only the expense of medical costs but also socioeconomic burden [1]. They often occur simultaneously as comorbidities and are collectively named "unified airway diseases." Indeed, asthma is the most important comorbidity of CRS [2, 3]. CRS is clinically divided into 2 groups according to the presence or absence of nasal polyps (NPs): CRS with and without NPs (CRSwNP and CRSsNP) [4]. The former is generally characterized by type 2-predominant tissue inflammation in Europe and the USA, while only 20–60% of NPs carry type 2 inflammatory signatures in Asian countries [5–11]. Meanwhile, an epidemiological study conducted in Japan has reported that prominent eosinophilic infiltration was observed in the NPs (≥15% eosinophils among inflammatory cells in NPs) in 97.4% of CRSwNP patients comorbid with asthma [7]. Endoscopic sinus surgery (ESS) is often performed in CRSwNP patients, though patients who have eosinophilic NPs (70/high-power field [HPF; ×400] in NPs) show often recurrence of NPs after ESS [2]. Thus, eosinophilic CRS (ECRS) is a clinical challenge not only in Europe and the USA but also in Asian countries. ESS may potentially be beneficial for comorbid asthma, as indicated by improved asthma-related quality of life (QoL) [12], decreased asthma severity scores [13], decreased inhaled corticosteroids (ICS) dose [13], and reduced number of asthma exacerbations [14–16]. This suggests that surgical intervention, particularly resection of eosinophilic polyps, is associated with the attenuation of type 2 lower airway inflammation in patients with asthma.

It is well known that periostin, mainly produced by lung fibroblasts [17] and airway epithelium [18] in response to interleukin (IL)-4 and IL-13, facilitates airway remodeling by binding other extracellular proteins including collagen [17] and mediating collagen synthesis and fibrogenesis [18]. Furthermore, it also induces chronic type 2 inflammation as a matricellular protein [19]. Periostin reflects the pathophysiology of type 2-driven allergic diseases such as asthma [20], CRS [21], and atopic dermatitis [19], along with blood eosinophils and fractional nitric oxide (FeNO) [22]. Although both increases and nonsignificant differences in levels of serum periostin between asthmatics and healthy subjects have been reported in different studies [20, 23], levels in asthmatic patients further increase upon having comorbid NPs [24, 25]. This indicates that serum periostin levels reflect the presence of NPs in asthmatic patients.

The aim of this study is to identify preoperative biomarkers that can predict reduction in asthma exacerbations following ESS. We hypothesized that high levels of preoperative serum periostin and the number of eosinophils in NPs could be indicators for the reduction in asthma exacerbations by ESS intervention.

Methods

This study is a post hoc analysis of our previous study that evaluated the pathophysiological link between upper and lower airways in CRS patients [26]. We prospectively recruited 56 CRS patients who were subjected to undergo ESS between October 2015 and December 2017 and followed them for 1 year after ESS. The patients were diagnosed as having asthma when they complained of asthma-related symptoms such as cough, dyspnea, chest tightness, and wheezing with the presence of clinical reversible airway obstruction or airway hyperresponsiveness to inhaled methacholine [27]. The diagnosis of CRS was made according to radiological and endoscopic findings with 2 or more physical symptoms (mucopurulent drainage, nasal obstruction, facial pain, and impaired sense of smell) lasting for 12 weeks or longer [28].

All patients underwent measurements of blood eosinophils, serum IgE, periostin, osteopontin, and YKL-40, and FeNO at enrollment, along with sinus CT scan, olfactory function testing assessed by Open Essence method (ranging from 0 to 12, lower scores indicate worse olfaction), CRS-related QoL questionnaire, Sino-nasal Outcome Test-22 [29], and pulmonary function testing. Tissue eosinophilia was also analyzed using resected sinus and NP samples. Patients with comorbid asthma also completed the Asthma Quality of Life Questionnaire (AQLQ) [30]. Patients were excluded if they were current smokers or had ceased smoking within the previous 6 months, had other pulmonary diseases including chronic obstructive pulmonary disease, took oral corticosteroids, or experienced an acute respiratory infection within 4 weeks prior to enrollment. We previously described this methodology in detail [26], except for the serum biomarker measures. Information for biomarker measurements, histological evaluation of resected sinus, and NP samples and evaluation of asthma-related QoL were described in online suppl. material; for all online suppl. material, see www.karger.com/doi/10.1159/000509253.

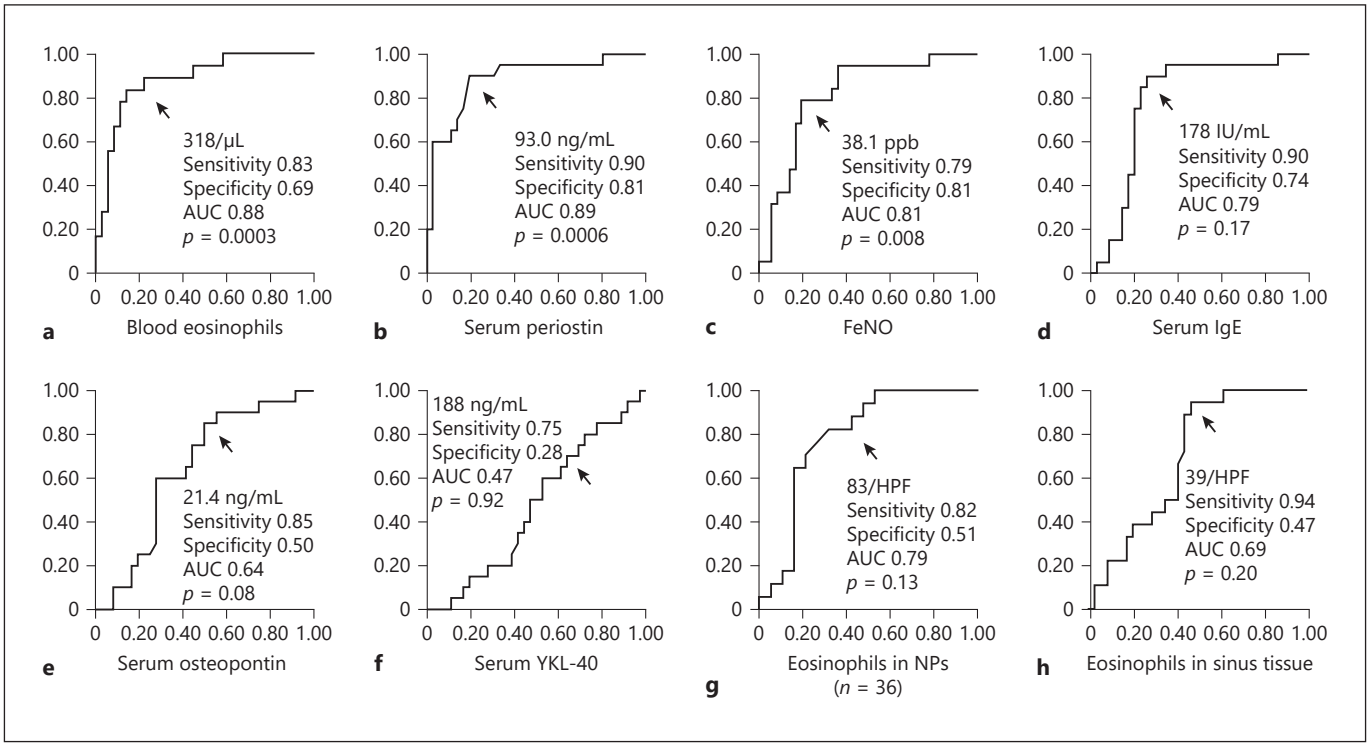

Fig. 1. Receiver operating characteristic curves for discriminating comorbid asthma among CRS patients.The sensitivity and specificity of blood eosinophils (**a**), serum periostin (**b**), FeNO (**c**), serum IgE (**d**), serum osteopontin (**e**), serum YKL-40 (**f**), and eosinophils in nasal polyps (**g**) and sinus tissue (**h**) are shown. One CRS patient with asthma failed to undergo the FeNO measurement because of an apparatus failure. Receiver operating characteristic analysis was applied to determine the accuracy of biomarkers for the diagnosis of comorbid asthma. FeNO, fractional nitric oxide; CRS, chronic rhinosinusitis.

This study was approved by the Ethics Committee of Nagoya City University (No. 1165) and was registered on the UMIN Clinical Trials Registry (Registry ID UMIN000018672). Written informed consent was obtained from all participants.

Definition of Asthma Exacerbations

Asthma exacerbations were defined as patients requiring oral corticosteroids for 3 or more days and/or intravenous corticosteroids for 1 or more days, or experiencing hospitalization due to asthma worsening in accordance with the ERS/ATS severe asthma guidelines[31].Thechangeinexacerbationnumber(Δexacerbations) with ESS intervention was calculated as follows: Δexacerbations = numbers of exacerbations for 1 year before ESS – those for 1 year after ESS.

Statistics

Data were analyzed using JMP 14.2 Start Statistics (SAS Institute Inc., Cary, NC, USA) and are presented as medians (5th percentile and 95th percentile) or *n* (%). Comparisons of upper/lower airway indices and biomarkers between the 2 groups (asthma vs. without asthma and nonexacerbators after ESS [Ex-group] vs. exacerbators after ESS [Ex + group]) were made using the Wilcoxon rank-sum test. The Wilcoxon single-rank test was adapted when biomarkers were compared between before and after ESS. For categorical variables, Fisher exact tests were applied. We investigated the accuracy of biomarkers for the detection of comorbid asthma among CRS patients and the prediction of exacerbation reduction following ESS using receiver operating characteristic (ROC) analysis. A p value ≤0.05 was considered significant when α error was set at 5%.

Spearman rank correlations were used to assess associations of preoperative upper/lower airway indices and biomarkers with exacerbation numbers for 1 year after ESS and Δexacerbations. When a ρ value showed ≥|0.40|, we considered this a meaningful correlation.

Results

Characteristics of the 56 CRS patients (20 with and 36 without asthma) are shown in online suppl. Table 1. Detailed information of the characteristics has been reported previously [26]. Age, sex, body mass index, CRS disease duration, and history of previous sinus surgery did not differ significantly between CRS patients with and without asthma. Seven participants experienced a recurrence of NPs, but no one required surgical intervention during the 1-year follow-up.

Table 1. Characteristics of asthmatic patients before and 1 year after ESS (n = 18)

	At enrollment	1 year after ESS	p value
ICS dose, μg, daily	400 (0, 1,360)	500 (0, 960)	0.33
Treatment steps, GINA 2/3/4, n (%)	3 (17)/6 (33)/9 (50)	1 (5)/5 (28)/12 (67)	0.08
Exacerbations (≥1/year), experienced, n (%)	7 (39)	8 (44)	0.63
Admission (≥1/year), experienced, n (%)	4 (33)	0 (0)	–
AQLQ, points	5.7 (4.5, 6.9)	6.4 (4.9, 7)	0.0005
FEV_1, %pred	85.9 (65.0, 103.2)	87.7 (64.6, 107.7)	0.67
Histological characteristics			
Eosinophils in NPs, /HPF[a]	123 (28, 447)	NA	–
Eosinophils in sinus tissue, /HPF	100 (36, 746)	NA	–
Biomarkers			
Blood eosinophils, /μL	570 (185, 1,271)	405 (136, 1,403)	0.09
Serum periostin, ng/mL	129 (81, 238)	118 (59, 289)	0.58
FeNO, ppb[a]	50.4 (25.6, 101.0)	34.4 (21.3, 157.3)	0.52

Data were expressed as mean (SD), otherwise median (5th percentile and 95th percentile) or n (%). ESS, endoscopic sinus surgery; ICS, inhaled corticosteroids; GINA, Global Initiative for Asthma 2015; HPF, high-power field; AQLQ, the Asthma Quality of Life Questionnaire; FeNO, fractional nitric oxide. [a] n = 17.

In the 20 patients with comorbid asthma, 17 regularly received inhaled corticosteroids with the median dose of 450 (0, 1,360) μg (fluticasone propionate equivalent). Remaining 3 (15%) patients used leukotriene receptor antagonists alone. None were taking oral corticosteroids or biologic treatments at enrollment. Asthma exacerbations requiring oral corticosteroids for 3 or more days and/or intravenous steroids for 1 or more days occurred in 8 (40%) patients (median 3 [1, 5]) within 1 year prior to enrollment, 5 of whom had experienced hospitalization (≥1/year) (median 1 [1, 3]).

The Accuracy of Biomarkers for the Detection of Comorbid Asthma among CRS Patients

Biomarker levels stratified by the presence or absence of asthma are presented in online supplementary Figure 1. Type 2-driven biomarkers such as blood eosinophils, serum IgE, periostin, and FeNO levels were significantly higher in CRS patients with asthma than in those without (online suppl. Fig. 1a–d; all $p < 0.01$). Meanwhile, serum osteopontin and YKL-40 levels were similar between the 2 groups (online suppl. Fig. 1e, f).

A ROC analysis revealed that blood eosinophils, serum periostin, and FeNO were sensitive biomarkers to discriminate between CRS patients with comorbid asthma and those without asthma, with high sensitivity and specificity (Fig. 1a–c; all $p < 0.01$). When CRS was histologically divided into eosinophilic (≥70/HPF in sinus tissue and/or NPs) and noneosinophilic (<70/HPF in sinus tissue and/or NPs) [2], similar trend was observed in both ECRS and non-ECRS for blood eosinophils and serum periostin levels (online suppl. Fig. 2).

Characteristics of Asthmatic Patients Compared between before and 1 Year after ESS

Eighteen out of 20 CRS patients with comorbid asthma were available for follow-up for 1 year after ESS (Table 1). All but 1 patient had NPs. Fourteen patients had eosinophilic NPs (≥70/HPF). Three patients who did not receive ICS at enrollment began taking them during the 1-year follow-up: 2 due to asthma exacerbations and one who switched from leukotriene receptor antagonists to ICS. The median dose of ICS at 1 year after ESS did not significantly differ from that at enrollment (p = 0.33). Asthma exacerbations requiring systemic corticosteroids occurred in 8 (44%) patients; 4 of whom had experienced exacerbations for the 2 consecutive years. All 3 patients with noneosinophilic NPs (<70/HPF) experienced asthma exacerbations following ESS. One also experienced a recurrence of NPs. The number of exacerbations was also similar between before and after intervention of ESS (Fig. 2a, b). Seven (39%) did not experience exacerbations for 2 consecutive years. The median number of Δexacerbations was 0 (−2, 4). It was declined by ESS in 5 patients, though 6 patients experienced exacerbations more often after ESS than before (Fig. 2c). In addition, ESS did not affect blood eosinophil count, serum periostin, or FeNO levels, or pulmonary function. Levels of serum periostin did not decline in

Table 2. Comparison of preoperative indices between patients with and without asthma exacerbation following ESS

	Ex– (n = 10)	Ex+ (n = 8)	p value
Clinical factors			
Age, years	63 (53, 70)	55 (29, 70)	0.25
Sex, female	3 (30)	2 (25)	>0.99
Body mass index, m^2/kg	24.0 (20.0, 27.5)	24.9 (21.3, 27.4)	0.32
Smoking history, ex	7 (70)	4 (50)	0.63
Duration of sinusitis, years	1 (1, 19)	1.5 (0.5, 15)	0.88
Asthma, years	4 (1, 19)	5.5 (0.5, 15)	0.56
ICS dose, μg	400 (0, 1,360)	450 (0, 640)	0.47
GINA treatment steps at enrollment, step 4	4 (40)	4 (50)	>0.99
Exacerbation prior to enrollment (≥1/year), experienced	3 (30)	4 (50)	0.63
Admission prior to enrollment (≥1/year), experienced	2 (20)	2 (25)	>0.99
Upper airway factors			
Previous ESS history, presence	0 (0)	3 (38)	0.07
Recurrence of NPs at 12 months after ESS	2 (20)	1 (13)	>0.99
SNOT-22, points	23 (6, 60)	36 (11, 66)	0.21
Lund-Mackay scores, points	15 (8, 20)	15 (10, 20)	0.50
Open Essence scores, points	3 (0, 8)	1 (0, 8)	>0.99
Lower airway factors			
AQLQ, points	5.8 (4.8, 6.9)	6.0 (4.1, 7.0)	0.40
FEV_1, %pred	85.7 (55.9, 110.4)	86.7 (67.0, 101.7)	0.96
Histological biomarkers			
Eosinophils in NPs, /HPF[a]	133 (83, 633)	100 (6, 400)	0.27
Eosinophils in sinus tissue, /HPF	113 (20, 487)	81 (61, 776)	0.82
Biomarkers at enrollment			
Blood eosinophils, /μL	538 (154, 1,550)	570 (190, 1,209)	0.82
Serum periostin, ng/mL	157 (66, 416)	105 (84, 152)	0.08
FeNO, ppb[a]	46.1 (27.9, 76.1)	54.0 (16.2, 175.5)	0.56

ESS, endoscopic sinus surgery; ICS, inhaled corticosteroids; GINA, Global Initiative for Asthma 2015; SNOT-22, Sino-nasal Outcome Test-22; AQLQ, the Asthma Quality of Life Questionnaire; FeNO, fractional nitric oxide; HPF, high-power field. [a] n = 17 (Ex–, n = 9).

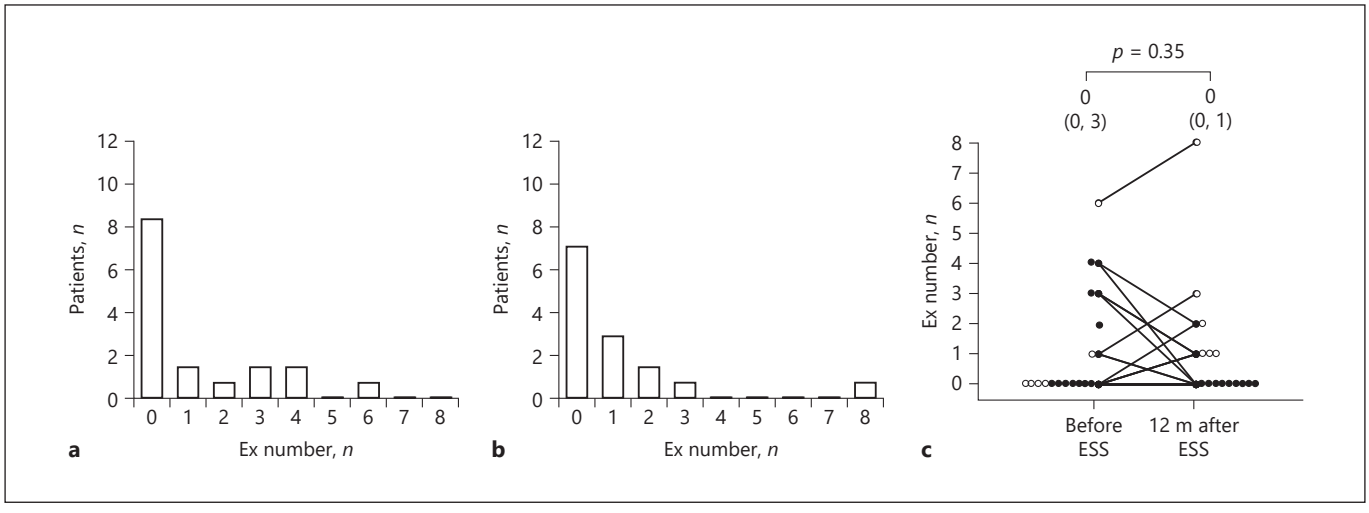

Fig. 2. The comparison of the number of exacerbations between before and 12 months after ESS. Histograms show the number of exacerbations before (**a**) and 12 months after ESS (**b**). **c** The number of exacerbations was compared between before and 12 months after ESS. Open circles show patients who experienced exacerbations more often after ESS than before. ESS, endoscopic sinus surgery; Ex number: the number of exacerbations; 12 m: 12 months.

Table 3. Correlation between preoperative indices and asthma exacerbations

	Exacerbations for 1 year after ESS		Δexacerbations[a]	
	ρ	*p* value	ρ	*p* value
Histological biomarkers				
Eosinophils in NPs, /HPF	−0.32	0.21	0.58	0.01
Eosinophils in sinus tissue, /HPF	0.33	0.32	0.05	0.84
Upper/lower airway indices and biomarkers at enrollment (before ESS)				
SNOT-22, points	0.33	0.18	−0.13	0.62
Lund-Mackay scores, points	0.10	0.69	0.28	0.27
Open essence scores, points	0.01	0.96	−0.31	0.22
AQLQ, points	−0.40	0.098	−0.20	0.42
FEV_1, %pred	−0.29	0.24	−0.03	0.91
Blood eosinophils, /μL	0.005	0.99	0.09	0.71
Serum periostin, ng/mL	−0.49	0.03	0.53	0.03
FeNO, ppb[b]	0.22	0.40	0.15	0.57

ESS, endoscopic sinus surgery; HPF, high-power field; GINA, Global Initiative for Asthma 2015; SNOT-22, Sino-nasal Outcome Test-22; AQLQ, the Asthma Quality of Life Questionnaire; FeNO, fractional nitric oxide. [a] Δexacerbations = numbers of exacerbations for 1 year before ESS – those for 1 year after ESS. Spearman rank correlation was used to assess associations of preoperative upper/lower airway indices and biomarkers with exacerbation numbers for 1 year after ESS and Δexacerbations. When a ρ value showed ≥ |0.40|, we considered that a meaningful correlation. [b] One patient failed to conduct the FeNO measurement because of apparatus failure.

7 patients 12 months after ESS. Among these patients, 5 experienced both or either of asthma exacerbations and NP recurrence ($n = 2$ for exacerbations, $n = 2$ for NP recurrence, and $n = 1$ for both). Meanwhile, no participants experienced hospitalization due to asthma during the 1-year follow-up. Furthermore, asthma-related QoL was significantly improved 1 year after ESS intervention (Table 2).

Comparison of Clinical Factors between Patients with and without Asthma Exacerbations following ESS

We stratified patients according to the presence or absence of asthma exacerbations during 1 year after ESS (Ex+ and Ex−groups). The 2 groups were similar for clinical preoperative characteristics such as age, sex, smoking history, disease duration of asthma and sinusitis, and the experience of exacerbations or admission in the previous year. Upper and lower airway indices were also similar between the 2 groups. Preoperative levels of serum periostin had a trend toward lower in the Ex+ group as compared with the Ex−group, but did not reach statistical significance (Table 2; $p = 0.08$).

Association of Upper/Lower Airway Indices and Biomarkers in CRS Patients with Asthma Exacerbations following CRS

Lastly, we investigated which upper/lower airway indices and biomarkers in CRS patients reflected asthma exacerbations following ESS (Table 3). Higher levels of preoperative serum periostin were associated with lower numbers of postoperative exacerbations and a reduced number of exacerbations following ESS (Table 3). In other words, high levels of preoperative serum periostin can predict patients who are likely to benefit from reduced asthma exacerbations following ESS. Furthermore, higher number of eosinophils in NPs was associated with reduced number of exacerbation following ESS (Table 3). However, ROC analysis indicated that either serum periostin or eosinophils in NPs did not predict the absence or reduction of exacerbations following ESS (online suppl. Fig. 3e). No upper/lower airway indices and biomarkers reflected the change in either asthma-related QoL or lung function following ESS (data not shown).

Discussion

There is no doubt that serum periostin, a downstream marker of IL-4/13-associated inflammation, is highly implicated in the pathophysiology of allergic diseases such as asthma and CRS, as demonstrated by previous studies [20, 24, 25, 32], along with blood eosinophils, serum IgE, and FeNO [22]. Although ESS may be effective in reducing asthma-related hospitalization [14, 16], there are no published data on the biomarkers that predict patients who

are expected to experience reduced asthma exacerbations after ESS, as far as we know. In the present study, we have demonstrated for the first time that increased levels of serum periostin and eosinophils in NPs are associated with the reduction in asthma exacerbations following ESS. Furthermore, we confirmed that serum periostin is a sensitive biomarker to detect comorbid asthma among CRS patients, along with blood eosinophil count and FeNO.

Serum periostin per se is not a biomarker reflecting asthma severity [23], though it is strongly correlated with other type 2-driven biomarkers such as sputum eosinophils and FeNO in severe asthma [23, 33]. In patients with severe asthma, serum periostin was the best predictor of persistent airway eosinophilia (sputum eosinophils ≥3% or submucosal eosinophilia ≥22/mm^2) despite the use of high-dose ICS (1,000 μg daily) [32]. Several previous reports including ours have also demonstrated that its levels are increased when CRS coexists in patients with asthma [20, 24, 25]. Notably, some studies show the association of serum periostin levels with NPs in CRS patients. We have demonstrated that serum periostin levels can discriminate comorbid CRS, especially CRS with NPs, among asthmatic patients [25]. Increased serum periostin are also associated with the postoperative recurrence of NPs after ESS [34]. In the present study, we have novelly revealed that preoperative increase in serum periostin levels is associated with the preventive effect of ESS for asthma exacerbations. The results of the present study further support the use of serum periostin as a biomarker evaluating type 2-predominant diseases, such as severe asthma [23] and unified airway diseases [25].

Blood eosinophils are the most commonly available surrogate biomarker of airway eosinophilia [22]. Blood eosinophil levels can indicate the presence of comorbid allergic rhinitis and CRS in patients with asthma [25]. However, preoperative blood eosinophil count did not predict the reduction in comorbid asthma exacerbations following ESS in CRS patients in the present study. Håkansson et al. [35] investigated differences in tissue inflammation in the lower airways among CRSwNP patients with or without asthma and healthy subjects. They demonstrated that CRSwNP with asthma had highest expression of IL-13 in bronchial tissue [35]. Meanwhile, IL-5 expression was similar among the 3 groups [35]. We have recently demonstrated that sputum periostin levels, but not sputum eosinophils or FeNO, are significantly increased in CRS patients than in healthy subjects even if asthma does not coexist [26]. These suggest that IL-13 and IL-4 may have a greater role in the development of type 2 lower airway inflammation than IL-5 in patients with unified airway diseases.

A systematic review and meta-analysis has clearly revealed that ESS has a beneficial effect on asthma control, decreasing the number of asthma exacerbations and use of antiasthma drugs such as oral corticosteroids, ICS, and bronchodilators [16]. Furthermore, following ESS, asthma symptoms are more prominently improved in patients with ECRS than in those with non-ECRS [36]. Resecting eosinophilic NPs may assist in attenuating type 2 lower airway inflammation. However, the association between recurrence of NPs following ESS and asthma exacerbations remains unclear.

Serum periostin levels did not decline by removal of NPs in our study. Recurrence of NPs may be reflected by the change in levels of serum periostin by ESS intervention. Ninomiya et al. [34] recently demonstrated that high serum periostin levels (≥115.5 ng/mL) could indicate not only NP eosinophilia but also an increased risk of postoperative recurrence of NPs in patients with CRSwNP. In our cohort, serum periostin levels increased at 12 months after ESS than before in all 3 patients with recurrent NPs following ESS. Another important fact is that periostin better reflects chronic type 2-predominant inflammation rather than acute inflammation [19]. According to a recent study by Kambara et al. [37], blood eosinophils and FeNO significantly decreased following ESS in CRSwNP [34]. Meanwhile, in patients with ICS-naïve asthma, the decreased rate of serum periostin at 24 weeks after the initiation of ICS treatment (equivalent to fluticasone propionate 400 μg daily) was numerically smaller than that of FeNO (5.4% for serum periostin vs. approximately 25% for FeNO) [38]. Serum periostin levels may not fluctuate by treatment intervention for the short term, unlike blood eosinophils and FeNO [37].

Effects of comorbid asthma and ESS on type 2-driven inflammation in CRS patients have been reported by using blood eosinophil, serum periostin, and FeNO [20, 24–26, 37, 39–41]. Serum periostin levels are significantly increased in asthmatics by having comorbid CRS [20, 24, 25], along with blood eosinophils [26] and FeNO [25, 26, 40]. Also, increased FeNO levels were correlated with radiological CRS severity in ECRS patients [37, 39]. We have already demonstrated that blood eosinophils, serum periostin, and FeNO are applicable for use in distinguishing comorbid CRS among patients with asthma [25]. In the present study, we have confirmed that all of blood eosinophils, serum periostin, and FeNO were useful for the detection of comorbid asthma among CRS patients. Furthermore, these 3 biomarkers are significantly declined by ESS in ECRS patients [37, 41], while we showed a trend only for eosinophils. These evidence support the exis-

tence of inflammatory link between upper and lower airway in the pathophysiology of unified airway diseases.

There are some limitations in this study. First, the sample size was small because we enrolled only patients who underwent ESS were eligible for this study because we sought to investigate histological association of NPs with asthma exacerbations following ESS. Sample size may have affected the predictive value of serum periostin or eosinophils in NPs for reduction of asthma exacerbations following ESS in ROC analysis (online suppl. Fig. 3e). Albeit such limitation, the present findings may be useful for clinicians to select patients who will benefit from ESS in terms of improved asthma control. Some clinicians are reluctant to perform ESS in CRS patients with comorbid asthma due to high recurrence rate of NPs after surgery [42]. Second, these findings may not be applicable in CRS patients whose condition is well controlled by medical therapies such as macrolides, antihistamines, and nasal corticosteroids. Although we did not succeed in following up all of the participants, we did collect data from 18 out of 20. Furthermore, all information regarding asthma including exacerbations was well evaluated on the basis of medical examinations by asthma specialists. To confirm the utility of serum periostin in CRS patients with asthma, a large study would be required.

In conclusion, evaluating preoperative serum periostin levels and the number of eosinophils in NPs may be helpful for clinicians to identify patients who are likely to benefit from reduced exacerbations following ESS in CRS patients with comorbid asthma. The present findings provide clinicians with the utility of serum periostin as a biomarker for the evaluation and management of comorbid asthma in CRS patients. Further studies involving larger cohort are necessary to confirm the utility of serum periostin in clinical practice of allergic diseases worldwide.

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Statement of Ethics

The authors declare that this research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This study was approved by the Ethics Committee of Nagoya City University (No. 1165) and was registered on the UMIN Clinical Trials Registry (Registry ID UMIN000018672). Written informed consent was obtained from all participants.

Conflict of Interest Statement

Y.K. reports research grants from Novartis Pharma and Mitsubishi Tanabe Pharma for the submitted work and grants from MSD and Kyowa Kirin corporations outside the submitted work. M.S. reports a research grant from Kobayashi Foundation for the submitted work. S.F. reports personal fees from AstraZeneca and Eli Lilly Japan outside the submitted work. H.O. reports research grant from Boehringer Ingelheim outside the submitted work. K.M. reports personal fees from Pfizer and Chugai Pharmaceutical outside the submitted work. T.O. reports personal fees from AstraZeneca, Eli Lilly Japan, Taiho Pharmaceutical, Pfizer, Chugai Pharmaceutical, MSD, Daiichi Sankyo, and Asahi Kasei Pharma and research grants and personal fees from Kyowa Hakko Kirin, Boehringer Ingelheim, Ono Pharmaceutical, and Novaltis outside the submitted work. K.I. reports research grants from Shino-Test Corporation for the submitted work. M.T. reports research grant from Pfizer outside the submitted work. A.N. reports personal fees from Astellas, AstraZeneca, Kyorin, GSK, MSD, Shionogi, Bayer, Sanofi, Taiho, and Boehringer Ingelheim and research grants from Astellas, Kyorin, Boehringer Ingelheim, Novartis, MSD, Daiichi Sankyo, Taiho, Teijin, Ono, Takeda, and Sanofi Pharmaceutical outside the submitted work.

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Author Contributions

Y.K. established the study design and contributed to the performance of diagnostic tests, collection of data, recruitment of patients, disease diagnosis and management, acquisition and interpretation of data, and drafting the manuscript. K.F., R.K., and N.T. contributed to the performance of diagnostic tests, collection of data, and acquisition and interpretation of data. S.F., T.U., T.T., H.O., K.M., Y.I., and T.O. contributed to the diagnostic tests, collection of data, and management of patients. J.O. and K.I. carried out the measurement of periostin. A.M. made specimens and assessed the infiltration of eosinophils in upper airway tissues. Y.O. contributed to assess the radiological severity of CRS. M.T. contributed to the recruitment of patients, disease diagnosis and management, and revision of the manuscript. M.S. and A.N. contributed to the recruitment of patients, disease diagnosis and management, interpretation of data, and revision of the manuscript.

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