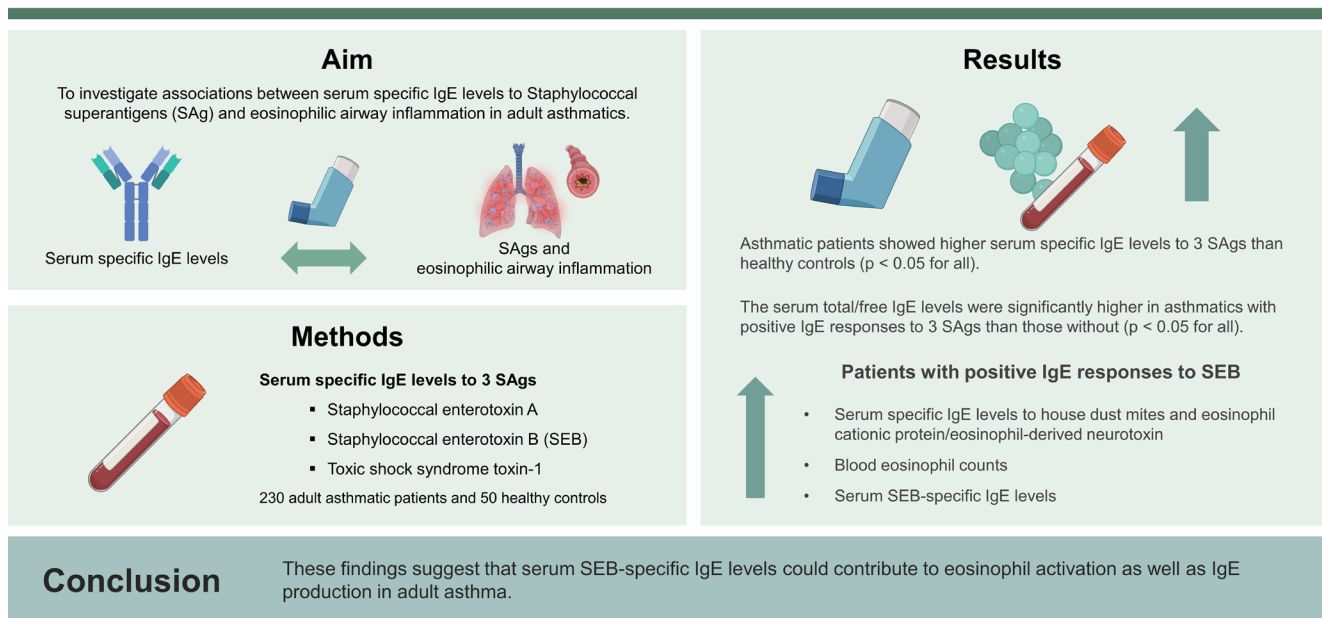# Association between specific IgE to staphylococcal enterotoxin B and the eosinophilic phenotype of asthma

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Association between specific IgE to staphylococcal enterotoxin B and the eosinophilic phenotype of asthma

Aim

To investigate associations between serum specific IgE levels to Staphylococcal superantigens (SAg) and eosinophilic airway inflammation in adult asthmatics.

Serum specific IgE levels ⟷ SAgs and eosinophilic airway inflammation

Methods

Serum specific IgE levels to 3 SAgs
- Staphylococcal enterotoxin A
- Staphylococcal enterotoxin B (SEB)
- Toxic shock syndrome toxin-1

230 adult asthmatic patients and 50 healthy controls

Results

Asthmatic patients showed higher serum specific IgE levels to 3 SAgs than healthy controls (p < 0.05 for all).

The serum total/free IgE levels were significantly higher in asthmatics with positive IgE responses to 3 SAgs than those without (p < 0.05 for all).

Patients with positive IgE responses to SEB
- Serum specific IgE levels to house dust mites and eosinophil cationic protein/eosinophil-derived neurotoxin
- Blood eosinophil counts
- Serum SEB-specific IgE levels

Conclusion These findings suggest that serum SEB-specific IgE levels could contribute to eosinophil activation as well as IgE production in adult asthma.

Background/Aims: Sensitization to staphylococcal superantigens (SAgs) could contribute to asthma severity. However, its relevance with eosinophilic phenotype has not yet been clarified. This study aimed to investigate associations between serum specific IgE levels to SAg and eosinophilic airway inflammation in adult asthmatics.

Methods: The serum specific IgE levels to 3 SAgs, including staphylococcal enterotoxin A (SEA) and B (SEB), and toxic shock syndrome toxin-1 (TSST-1) were measured by ImmunoCAP in 230 adult asthmatic patients and 50 healthy controls (HCs). Clinical characteristics and laboratory parameters, including serum total/free IgE, and 2 eosinophil-activation markers, eosinophil cationic protein (ECP), and eosinophil-derived neurotoxin (EDN), were analyzed according to blood eosinophil counts (BEC; 150 cells/μL) and serum specific IgE levels to 3 SAgs (0.35 kU/L).

Results: Asthmatic patients showed higher serum specific IgE levels to 3 SAgs than HCs ($p < 0.05$ for all). The serum total/

free IgE levels were significantly higher in asthmatics with positive IgE responses to 3 SAgs than those without ($p < 0.05$ for all). There were no significant differences in clinical parameters including age, asthma severity, comorbidities, or smoking according to IgE responses to 3 SAgs. Patients with positive IgE responses to SEB (not to SEA/TSST-1) had higher serum specific IgE levels to house dust mites and ECP/EDN as well as higher BEC with positive correlations between serum SEB-specific IgE levels and BEC/ECP/EDN ($p < 0.05$ for all).

Conclusions: These findings suggest that serum SEB-specific IgE levels could contribute to eosinophil activation as well as IgE production in adult asthma.

Keywords: Asthma; Eosinophil; IgE; *Staphylococcus aureus*; Superantigen

INTRODUCTION

Asthma is characterized by chronic airway inflammation with increasing prevalence and economic burdens, impairing the quality of life in patients [1,2]. Due to its heterogeneity, there have been constant attempts to establish asthma phenotypes or endotypes for understanding underlying pathogenic mechanisms [3]. For decades, asthma has commonly classified into type 2 (T2)-high and T2-low phenotypes based on immunologic mechanisms [4], where eosinophils are major effector cells responsible for driving T2 airway inflammation and remodeling by releasing interleukin (IL)-4, IL-5, and IL-13 and granule proteins, such as eosinophil cationic protein (ECP) and eosinophil-derived neurotoxin (EDN), via interactions among diverse immune cells including T helper (Th) 2 cells, group 2 innate lymphoid cells (ILC2), B cells, and mast cells [5].

Staphylococcus aureus is a commensal gram-positive bacterium mainly found in human skin tissues and upper respiratory tract [6,7]. However, *S. aureus* can be pathogenic as it releases several virulent factors, such as staphylococcal enterotoxins (SEs) and toxic shock syndrome toxin-1 (TSST-1), which also act as superantigens (SAgs), contributing to IgE-mediated responses in patients with atopic dermatitis and upper airway disease such as chronic rhinosinusitis and nasal polyps [8-10]. Regardless of antigen specificity, SAgs can directly activate T cells by linking their T cell receptors to class II major histocompatibility complex molecules on antigen-presenting cells, resulting in explosive release of T2 cytokines (IL-4, IL-5, and IL-13), which enhance eosinophilic inflammation and IgE production [11,12]. Recently, several studies have shown that SE sensitization is one of the environmental risk factors responsible for the development of asthma [13]. In particular, SE sensitization is associated with lower lung functions, higher blood/sputum eosinophil counts, and serum ECP levels [14-16], suggesting the role of IgE-sensitization to SE in eosinophilic phenotypes or disease severity [17].

Despite increasing evidence for the pathogenic role of staphylococcal SAgs in asthma, their relevance with eosinophilic airway inflammation has not yet been fully understood. Therefore, we evaluated clinical relevance of IgE-sensitization to 3 staphylococcal SAgs (SEA, SEB, and TSST-1) in association with eosinophilic inflammatory parameters in adult asthmatics in clinical practice.

METHODS

Patient recruitment

In this study, 230 adult asthmatic patients (over 20 years old) and 50 adult healthy controls (HCs) were enrolled. All the study subjects submitted written informed consent. The study was approved by the Institutional Review Board of Ajou University Hospital (AJIRB-GEN-SMP-13-108). The sera were collected at initial diagnosis and kept in a frozen state at -70°C until ELISA or immunoCAP assays were performed.

Evaluation of clinical parameters

In this study, asthmatic patients were diagnosed by the allergy specialists based on clinical histories and according to the recent GINA guideline [18]. Asthmatics who had used systemic steroids were excluded from this study. Atopy was defined as at least one positive result in skin prick tests for common inhaled allergens (Bencard, Bradford, UK), including 2 house dust mites (*Dermatophagoides pteronyssinus* [Dp] and *Dermatophagoides farinae* [Df]). The presence of chronic rhinosinusitis and nasal polyp was evaluated by clin-

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ical symptoms, radiologic findings (paranasal sinus X-rays and/or CT scans), and/or rhinoscopy. The diagnosis of atopic dermatitis and chronic urticaria were assessed by the allergists. Severe asthma was defined based on the guidelines of the European Respiratory Society and American Thoracic Society [19]. Clinical and immunologic parameters, including blood/sputum eosinophil counts, were assessed at the initial diagnosis. The degree of airway obstruction was examined using spirometry and airway hyperresponsiveness by methacholine bronchial challenge tests. The concentrations of serum total IgE as well as SEA-, SEB-, and TSST-1-specific IgE were measured using the ImmunoCAP system (ThermoFisher Scientific, Waltham, CA, USA). SAg-specific IgE levels > 0.35 kU/L were considered positive. The serum free IgE levels were measured by ELISA as previously described [20]. The serum levels of ECP and EDN were measured by ELISA (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's recommendations.

Statistical analysis

All the statistical analyses were performed using IBM SPSS software, version 26.0 (IBM Corp., Armonk, NY, USA). All data are presented as mean ± standard deviation. Group comparisons were made by Student's t-test and chi-square test. To analyze correlations between 2 variables, Spearman's rank correlation was conducted. p values of < 0.05 were considered statistically significant. GraphPad Prism 8.0 software (GraphPad Inc., San Diego, CA, USA) was used to create graphs.

RESULTS

Serum specific IgE levels to SEA, SEB, and TSST-1 in adult asthmatics

The clinical characteristics of the study subjects are summarized in Table 1. Atopy prevalence and male ratio as well as serum SEA-, SEB, and TSST-1-specific IgE levels were significantly higher in asthmatic patients than in HCs ($p < 0.05$ for all) as shown in Table 1.

Comparisons between SAg-specific IgE levels according to blood eosinophil counts

When asthmatic patients were divided into the high-eosinophil (≥ 150 cells/μL) and low-eosinophil groups (< 150 cells/μL), significantly higher serum levels of ECP, EDN, and IgE specific to Dp and Df were noted in the high-eosinophil group than in the low-eosinophil group ($p < 0.05$ for all) as depicted in Table 2. However, these 2 groups were not statistically different in terms of age, sex, atopy rate, immunologic parameters (such as serum total and free IgE levels), or FEV_1 (%) and PC20 values. Nevertheless, both se-

Table 1. Demographic data from the study subjects

Variable	Healthy controls (n = 50)	Asthmatic patients (n = 230)	p value
Age (yr)	45.2 ± 11.5	44.3 ± 13.3	0.625
Sex, female	41 (82.0)	150 (65.2)	0.021
Atopy	16 (32.0)	140 (60.9)	0.001
Serum ECP (ng/mL)	ND	29.6 ± 35.9	ND
Serum EDN (ng/mL)	ND	45.3 ± 29.9	ND
Specific IgE levels to			
SEA (kU/L)	0.06 ± 0.17	0.18 ± 0.48	0.010
SEB (kU/L)	0.09 ± 0.37	0.26 ± 0.68	0.043
TSST-1 (kU/L)	0.11 ± 0.24	0.52 ± 1.40	0.002
FEV1 (%)	ND	89.5 ± 19.4	ND
PC20 methacholine (mg/mL)	ND	12.2 ± 11.3	ND

Values are presented as number (%) for categorical variables and as mean ± standard deviation for continuous variables.
ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; SEA, staphylococcal enterotoxins A; SEB, staphylococcal enterotoxin B; TSST-1, toxic shock syndrome toxin-1; FEV1, forced expiratory volume in 1 s; PC20, provocation concentration of methacholine required to reduce FEV1 by 20% from the baseline value; ND, no data.
p values were obtained by Pearson's chi-squared test for categorical variables and by Student's t test for continuous variables.

rum SEA- and SEB-specific IgE levels were significantly higher in the high-eosinophil group than in the low-eosinophil group ($p = 0.009$ and $p = 0.004$, respectively). Furthermore, IgE-sensitization rates to SEA and SEB were greater in the high-eosinophil group than in the low-eosinophil group ($p = 0.024$ and $p = 0.008$, respectively; Table 3), while no differences were noted in serum TSST-1-specific IgE levels or sensitization rates to TSST-1 between the 2 groups.

Associations between SAg-specific IgE levels and eosinophilic inflammatory markers

The study further classified asthmatic patients to the SAg-positive and SAg-negative groups (> 0.35 kU/L and ≤ 0.35 kU/L, respectively) according to positivity for IgE responses to 3 SAgs. As a result, there were no significant differences in clinical characteristics between the 2 groups, except sex proportion and prevalence of atopy or atopic dermatitis. The proportion of male patients was significantly higher in the SEB-positive and TSST-1-positive groups than

in corresponding counterparts ($p = 0.001$ and $p = 0.026$, respectively). Moreover, the presence of atopy was higher in the TSST-1-positive group than in the TSST-1-negative group while that of atopic dermatitis was lower in the SEA-positive group than in the SEA-negative group ($p = 0.001$ and $p = 0.036$, respectively) as described in Table 4. When laboratory parameters were compared according to the positivity of IgE responses to 3 SAgs, the serum levels of total and free IgE as well as Dp-specific IgE were higher in the SAg-positive groups than in the SAg-negative groups ($p < 0.05$ for all). Although the serum Df- and Dp-specific IgE levels were higher in the SEB-positive group than in the SEB-negative group ($p = 0.020$ and $p = 0.029$), no differences were found between the SEA-positive and SEA-negative groups or between the TSST-1-positive and TSST-1-negative groups. Moreover, peripheral eosinophil counts and serum ECP and EDN levels were significantly higher in the SEB-positive group than in the SEB-negative group ($p < 0.05$ for all), albeit not significantly different between the SEA-positive

Table 2. Comparison of clinical characteristics according to blood eosinophil counts in asthmatic subjects

Variable	TEC ≥ 150 (n = 102)	TEC < 150 (n = 95)	p value
Age (yr)	45.6 ± 12.4	42.7 ± 14.0	0.135
Sex, female	60 (58.8)	67 (70.5)	0.086
Atopy	68 (66.7)	54 (56.8)	0.156
ECP (ng/mL)	37.7 ± 40.8	17.9 ± 13.5	0.001
EDN (ng/mL)	41.7 ± 22.3	29.9 ± 8.5	0.016
Total IgE (kU/L)	395.9 ± 594.2	253.4 ± 581.1	0.092
Free IgE (kU/L)	433.2 ± 613.7	242.6 ± 262.2	0.180
IgE to Dp (kU/L)	9.9 ± 24.4	3.9 ± 12.8	0.038
IgE to Df (kU/L)	15.1 ± 29.7	6.6 ± 18.6	0.021
Lung functions			
FEV1 (%)	86.0 ± 20.2	93.6 ± 17.5	0.059
PC20 methacholine (mg/mL)	9.9 ± 10.7	12.5 ± 10.1	0.309
Positive IgE response to			
SEA	17 (16.7)	6 (6.3)	0.024
SEB	26 (25.5)	10 (10.5)	0.008
TSST-1	27 (26.5)	20 (21.1)	0.373

Values are presented as number (%) for categorical variables and as mean ± standard deviation for continuous variables.

TEC, total eosinophil count; ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; Dp, *Dermatophagoides pteronyssinus*; Df, *Dermatophagoides farinae*; FEV1, forced expiratory volume in 1 s; PC20, provocation concentration of methacholine required to reduce FEV1 by 20% from the baseline value; SEA, staphylococcal enterotoxins A; SEB, staphylococcal enterotoxin B; TSST-1, toxic shock syndrome toxin-1; SAgs, staphylococcal superantigens.

SAg-specific IgE levels > 0.35 kU/L were considered positive.

p values were obtained by Pearson's chi-squared test for categorical variables and by Student's t-test for continuous variables.

Table 3. Comparison of clinical characteristics according to serum specific IgE levels to 3 SAgs in asthmatic patients

Variable	SEA > 0.35 (n = 26)	SEA ≤ 0.35 (n = 204)	p value	SEB > 0.35 (n = 42)	SEB ≤ 0.35 (n = 188)	p value	TSST-1 > 0.35 (n = 55)	TSST-1 ≤ 0.35 (n = 175)	p value
Age (yr)	47.3 ± 11.5	43.9 ± 13.5	0.222	43.8 ± 11.8	44.4 ± 13.6	0.766	42.7 ± 12.4	44.7 ± 13.6	0.332
Sex, female	16 (61.5)	134 (65.7)	0.676	18 (42.9)	131 (69.9)	0.001	29 (52.7)	121 (69.1)	0.026
Atopy (%)	18 (69.2)	122 (59.8)	0.354	26 (61.9)	114 (60.8)	0.879	44 (80.0)	96 (54.9)	0.001
CRS (%)	26 (100.0)	155 (76.0)	0.221	34 (81.0)	150 (80.0)	> 0.999	48 (87.5)	135 (77.3)	0.536
Nasal polyp (%)	33.3	32.4	0.920	28.6	31.4	0.885	28.6	34.5	0.701
Paranasal sinusitis (%)	66.7	48.6	0.685	40.0	52.8	0.776	36.4	56.7	0.371
Atopic dermatitis (%)	8.7	29.3	0.036	22.9	27.5	0.569	35.6	24.5	0.141
Chronic urticaria (%)	33.3	50.0	0.150	48.4	48.7	0.973	51.2	47.3	0.653
Smoking (%)	40.0	29.3	0.486	42.9	28.6	0.287	45.0	26.4	0.110
Severe asthma (%)	6.7	25.7	0.103	33.3	21.4	0.219	29.0	21.5	0.391
FEV1 (%)	90.5 ± 16.0	89.4 ± 19.9	0.861	90.6 ± 24.2	89.1 ± 18.5	0.803	86.0 ± 19.4	90.5 ± 19.5	0.331
PC20 methacholine (mg/mL)	11.4 ± 10.8	12.4 ± 11.5	0.802	11.3 ± 10.0	12.2 ± 11.7	0.757	10.0 ± 11.3	12.9 ± 11.3	0.309
Oral corticosteroid for 6 months (mg)	5.0 ± 13.8	4.7 ± 10.4	0.958	3.5 ± 7.9	13.5 ± 30.0	0.379	4.7 ± 14.4	5.9 ± 10.1	0.786

Values are presented as number (%) for categorical variables and as mean ± standard deviation for continuous variables.

SEA, staphylococcal enterotoxins A; SEB, staphylococcal enterotoxin B; TSST-1, toxic shock syndrome toxin-1; CRS, chronic rhinosinusitis; FEV1, forced expiratory volume in 1 s; PC20, provocation concentration of methacholine required to reduce FEV1 by 20% from the baseline value; SAgs, staphylococcal superantigens.

SAg-specific IgE levels > 0.35 kU/L were considered positive.

p values were obtained by Pearson's chi-squared test for categorical variables and by Student's t-test for continuous variables.

Table 4. Comparison of laboratory parameters according to serum specific IgE levels to SAgs in asthmatic patients

Variable	SEA > 0.35 (n = 26)	SEA ≤ 0.35 (n = 204)	p value	SEB > 0.35 (n = 42)	SEB ≤ 0.35 (n = 188)	p value	TSST-1 > 0.35 (n = 55)	TSST-1 ≤ 0.35 (n = 175)	p value
Total IgE (kU/L)	911.5 ± 902.0	247.6 ± 455.7	0.001	770.2 ± 779.5	226.2 ± 457.8	0.001	706.3 ± 903.7	206.9 ± 334.3	0.001
Free IgE (kU/L)	965.5 ± 1,066.0	300.0 ± 354.3	0.001	880.1 ± 782.1	227.6 ± 275.6	0.004	611.7 ± 422.3	309.1 ± 499.3	0.032
IgE to Dp (kU/L)	17.3 ± 33.2	6.2 ± 16.6	0.007	16.0 ± 26.8	5.4 ± 16.7	0.029	12.1 ± 23.7	6.0 ± 17.9	0.094
IgE to Df (kU/L)	22.6 ± 36.3	10.4 ± 23.8	0.107	23.5 ± 35.1	9.0 ± 21.9	0.020	18.9 ± 31.2	9.7 ± 23.7	0.058
TEC (/μL)	326.0 ± 293.9	240.6 ± 263.2	0.150	323.4 ± 307.5	225.9 ± 242.0	0.042	271.6 ± 254.7	244.0 ± 271.9	0.589
Sputum eos (%)	12.5 ± 27.6	2.2 ± 12.2	0.275	9.5 ± 25.5	2.4 ± 12.2	0.343	5.9 ± 20.1	2.8 ± 13.4	0.458
ECP (ng/mL)	38.4 ± 47.2	25.8 ± 28.2	0.245	45.9 ± 58.4	23.7 ± 20.4	0.042	32.6 ± 38.9	25.6 ± 28.1	0.270
EDN (ng/mL)	55.0 ± 31.1	33.4 ± 11.9	0.092	47.6 ± 26.5	32.2 ± 10.0	0.037	45.8 ± 29.3	33.6 ± 11.0	0.163

Values are presented as mean ± standard deviation for continuous variables.

SEA, staphylococcal enterotoxins A; SEB, staphylococcal enterotoxin B; TSST-1, toxic shock syndrome toxin-1; Df, Dermatophagoides farinae; Dp, Dermatophagoides pteronyssinus; TEC, total eosinophil count; eos, eosinophils; ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; SAgs, staphylococcal superantigens.

SAg-specific IgE levels > 0.35 kU/L were considered positive.

p values were obtained by Pearson's chi-squared test for categorical variables and by Student's t-test for continuous variables.
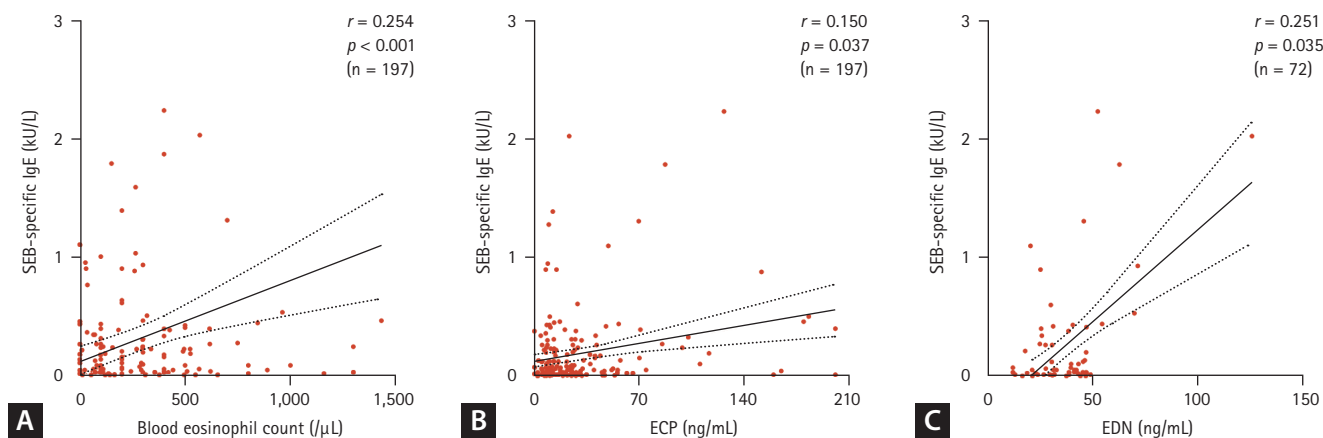
Figure 1. Correlations between (A) serum SEB-specific IgE levels, (B) blood eosinophil counts, and (C) serum ECP/EDN levels. Data are presented as Spearman's rank correlation coefficient r (*p* value). SEB, staphylococcal enterotoxin B; ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin.

and SEA-negative groups, and between the TSST-1-positive and TSST1-negative groups. In addition, serum SEB-specific IgE levels were positively correlated with blood eosinophil counts as well as with serum ECP and EDN levels in asthmatic patients (r = 0.254, *p* < 0.001; r = 0.150, *p* = 0.037; and r = 0.251, *p* = 0.035, respectively) (Fig. 1), while no significant correlations were noted in SEA- or TSST1-sensitized patients.

DISCUSSION

SAgs can activate various immune cells, such as T cells, B cells, mast cells, eosinophils, and epithelial cells, resulting in massive production of cytokines and granule proteins as well as polyclonal IgE formation, contributing to asthma pathogenesis [21]. Among them, SEB, a major enterotoxin of *S. aureus*, amplifies T2 immune responses by inducing the production of T2 cytokines including IL-4, IL-5, and IL-13, leading to blood and airway eosinophilia [22,23]. Previous studies have demonstrated that IgE-sensitization to SEs could increase IgE production and blood/sputum eosinophil counts in association with severe asthma and late-onset elderly asthma [14,16]. In this study, significantly higher prevalence rates of serum specific IgE to 3 kinds of staphylococcal SAgs (SEA, SEB, and TSST-1) were associated with increased serum total/free IgE levels in adult asthmatics. Furthermore, significant correlations were noted between serum specific IgE levels to SEB (not to SEA or TSST-1) and higher blood eosinophils as well as higher serum ECP and EDN levels in

adult asthmatics. These findings demonstrate that, among 3 staphylococcal SAgs, sensitization to SEB could be mainly involved in T2/eosinophilic inflammation, presenting the eosinophilic phenotype of asthma.

SAgs are known to induce B cell expansion and activation in response to T2 cytokines, promoting class switching to IgE and polyclonal IgE production [24]. Several studies have shown that bronchial exposure to SAg elevates serum total IgE and allergen-specific IgE in an allergic asthma mouse model sensitized by ovalbumin (OVA) [23,25]. Moreover, sensitization to SEs, not to aeroallergens, such as grass pollen or house dust mites, was closely related to higher total serum IgE and disease severity characterized by frequent asthma exacerbations and lung function decline [26,27]. The present study demonstrated that asthmatic patients with positive IgE responses to staphylococcal SAgs had higher serum total/free IgE levels, suggesting that IgE sensitization to SAgs could promote IgE production in B cells. Increased IgE activates diverse immune cells including mast cells, basophils, and dendritic cells by binding FcεR I on their surfaces, which enhances T2/eosinophilic responses [28]. Our previous study reported that high serum free IgE levels could be a more reliable marker than serum total IgE levels for predicting T2 inflammation along with other traditional T2 markers, such as blood eosinophilia, and for monitoring therapeutic responses after omalizumab treatment in asthmatic patients [20]. Therefore, sensitization to 3 staphylococcal SAgs could contribute to polyclonal B cell activation, leading to increased serum total/free IgE levels, where anti-IgE antibody may be a therapeutic strategy in

SAg-sensitized asthmatics.

There is accumulating evidence that sensitization to staphylococcal SAgs increases the risk of severe asthma by inducing persistent Th2/eosinophilic inflammation in asthmatic airways [13]. Severe asthma is characterized by persistent blood eosinophilia and uncontrolled symptoms, such as frequent asthma exacerbations and progressive lung function decline, even on medication with high-dose inhaled corticosteroids with an additional controller and/or systemic corticosteroid [19]. In addition, the levels of serum ECP and EDN are useful biomarkers for eosinophil activation and degranulation, contributing to asthma severity in adult asthmatics [29,30]. Furthermore, blood eosinophil counts are easily measurable indicators for predicting disease severity, exacerbation frequency, and impaired lung function [31,32], while no associations were found in recent studies [33,34]. In the present study, positive IgE responses to staphylococcal SAgs were not associated with asthma severity, lung function parameters, or asthma comorbidities. However, IgE specific to SEB (not to SEA or TSST-1) was significantly associated with blood eosinophilia and increased eosinophil activation/degranulation, indicating that IgE sensitization to SEB may contribute to eosinophilic inflammation in asthmatic airways. Previous *in vivo* studies have shown that bronchial exposure to SEB (not to SEA or TSST-1) induced allergic airway inflammation with increased eosinophil counts in bronchoalveolar lavage fluid as well as serum total IgE and OVA-specific IgE in OVA-sensitized mice [25]. Moreover, several *in vitro* studies have demonstrated SAg induced the formation of eosinophil extracellular eosinophilic traps in defected airway epithelium, enhancing T2/eosinophilic responses via ILC2 activation, which is the major cause of persistent airway inflammation and steroid resistance in eosinophilic asthma [35-37]. However, some studies have reported no association between IgE sensitization to SAgs and asthma severity or disease control [38-41]. This controversy may be attributed to variations in positive cutoff values (> 0.35 or > 0.1 kU/L) or study populations. Thus, further investigations are needed to elucidate pathogenic mechanisms of how specific IgE to SEB (not to SEA or TSST-1) contributes to eosinophilic inflammation in asthmatic airways. Taken together, the present study suggests that high serum specific IgE to SEB may be a potential biomarker for T2/eosinophilic inflammation in asthma. Further studies using standardized cutoff values are needed to confirm our results.

There are some limitations in this study. First, the number of subjects enrolled in the study was not large enough to represent adult asthmatics having various phenotypes. Furthermore, there were missing values in some variables as some patients did not fully perform all the laboratory tests at initial visit. However, we evaluated IgE-sensitization to 3 kinds of major SAgs in the sera of 230 adult asthmatics and analyzed their associations with various clinical/immunologic/inflammatory parameters. Secondly, this is a cross-sectional study, not a longitudinal outcome study tracking the endotypes of asthma. Further investigations are needed to evaluate the role of specific IgE to these 3 SAgs in the long-term outcome model of adult asthma that includes therapeutic responses.

In conclusion, we suggest that IgE-sensitization to 3 staphylococcal SAgs could increase serum IgE levels regardless of atopy status, and that IgE-sensitization to SEB may enhance eosinophilic inflammation in adult asthmatics.

KEY MESSAGE

1. IgE-sensitization to 3 staphylococcal SAgs increases serum IgE levels via stimulating B cells regardless of atopic status.
2. IgE-sensitization to SEB enhances eosinophilic inflammation in adult asthma.
3. IgE is a major therapeutic target for controlling eosinophilic airway inflammation.

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