

# The Possible Association Of Staphylococcus Enterotoxin B As A Cause Of Asthma In The Presence Of Sinusitis

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## Abstract

The prevalence of asthma is increasing in the world. The pathogenesis needs to be further understood. Asthma is closely related with sinusitis, but the detailed mechanisms are yet not clear. Eighty-five patients with sinusitis and asthma underwent functional endoscopic sinus surgical treatment and serum antibodies and cytokines were measured. Fifty-one of 85 patients with high serum anti-Staphylococcus enterotoxin B (SEB) antibody before treatment obtained satisfactory results for both sinusitis and asthma. The high level of Th2 cytokine IL-4 was down regulated to the levels of normal controls after sinus surgery. Thirty-four of 85 patients did not show high serum anti-SEB antibody before sinus surgery and did not show much improvement in their asthmatic symptoms although sinusitis symptoms were resolved by sinus surgery. The present study indicates that bacterial superantigen SEB (in the sinuses) plays a crucial role in lower airway hypersensitivity.

## INTRODUCTION

The prevalence of airway allergy is increasing especially in the last decade. The pathogenesis of this disorder is still to be understood although a great advance has been made in this area. In the past 16 years, over 2000 patients with chronic rhinosinusitis (CRS) visited our department and received treatment of medicine or functional endoscopic sinus surgery (FESS). Some patients with both CRS and asthma, the clinical symptoms of both CRS and asthma were greatly improved after FESS. Clinical experience has implicated a close relationship between sinusitis and asthma<sup>1, 2</sup>. Some patients who suffer from asthma or allergic rhinitis report pre-existing sinusitis. Accumulated clinical data demonstrate that surgical and non-surgical sinus management can improve sinus and asthma symptoms<sup>1, 3</sup>, but the mechanism is yet to be understood. Asthma is a significant health problem in the world, with an ever-increasing morbidity and mortality, and economic impact through both direct and indirect costs. There are still no satisfactory therapies in the treatment of asthma despite the many new pharmaceutical products come out every year. Now that the collective evidences demonstrate that satisfactory results have been achieved in some patients with both sinusitis and asthma through treatment of their sinusitis, it is imperative to understand the mechanisms in order to improve this therapy and obtain more satisfactory results.

Chronic rhinosinusitis is a multi-variant disease. Bacterial infection is the accepted cause of acute sinusitis in most circumstances, but the causes of chronic sinusitis are more complicated. Staphylococcus aureus (*S. aureus*) is a common pathogen that contributes to both acute and chronic sinusitis<sup>4</sup>. *S. aureus* produces toxins which may act as superantigens which may affect lymphocyte upregulation and therefore, have strong immune activity. It produces toxins such as SEB, SEA and TSST-1, which possess strong immune activity to affect immune system. Reports demonstrate high levels of SEB, SEA and TSST-1 in nasal secretions of patients with allergic rhinitis and asthma, as well as increased SEB and SEA specific serum IgE antibody levels.<sup>5</sup> It is not clear how these toxins contribute to airway hypersensitivity. It is known that these toxins participate in airway immune reactions during sinusitis by contaminating airway mucosa through secretions from the sinus ostia. SEB has the potential to increase airway epithelial barrier permeability, facilitating macromolecular protein antigen crossing of the epithelium to activate in subepithelium T cells.<sup>6</sup>

In addition, enterotoxins can be found in cases of toxic shock syndrome.<sup>7</sup> and have been implicated in the autoimmune disease, rheumatoid arthritis.<sup>8</sup> Enterotoxin B is synthesized as a precursor protein of 266 amino acids. This precursor is then activated during excretion of the protein by cleavage of an N-terminal portion of the molecule. The

active enterotoxin B is a single 239 amino acid chain of molecular weight 28,000 daltons and isoelectric point of 8.6.<sup>9</sup> SEB is a superantigen and possesses powerful immune regulatory capability that results in increased T cell activation and proliferation. SEB-treated Balb/c mice displayed a dose-dependent colonic inflammation.<sup>10</sup> SEB can also induce colonic epithelial barrier dysfunction<sup>11</sup> that may promote exogenous antigens, microbial products and other noxious substances uptake into the intestinal tissue to have opportunity to contact immune cells and initiate appropriate immune reactions.

We hypothesized that SEB that released from chronic sinusitis played an important role in the pathogenesis of airway allergy. In this study, a group of patients with both chronic sinusitis and allergic asthma were treated with functional sinus endoscopic surgery. Levels of SEB, as well as IL-4 and IFN- $\gamma$  were evaluated for all patients before and after sinus surgery, and were compared with clinical symptom improvements. The results showed improvements of asthmatic symptoms significantly correlated with changes of SEB and cytokines levels.

## **MATERIALS AND METHODS**

### **PATIENTS**

Eighty-five patients with both chronic sinusitis and chronic asthma (41 females and 44 males, ranging from 19 to 58 years with a mean age of 33.54 years) were selected for this study. Eighty-one out of 85 treated patients completed the one-year follow-up visit. On admission the written consent was obtained from each parent whom was requested to complete a questionnaire about recent or recurrent hospitalization, visits to the health care facilities, antibiotic therapy, and surgery within the previous 6 months. Diagnosis of chronic sinusitis was made on the basis of at least a one-year history of clinical symptoms including purulent nasal and postnasal secretions, middle meatus purulent secretions, and CT scan showing evidence of maxillary sinusitis or/and ethmoid sinusitis. All patients tried different medical treatments and did not obtain satisfactory results and required surgical treatment. These patients also underwent routine physical examinations upon admittance. This study was approved by the Ethic Committee of the First Hospital, Shanxi Medical University.

All patients also suffered from perennial asthma. Among them, 51 patients' asthma symptoms occurred after their sinusitis. The diagnosis of asthma was based on the

guidelines provided in ref<sup>12</sup>. The history of asthmatic symptoms included episodic dyspnea and wheezing. These symptoms could be controlled by inhaling  $\beta_2$ -adrenoreceptor agonists, or theophylline preparations. Lung function tests were performed for patients with asthma before and after sinus surgery as well as at follow-up visits. Exercise-induced bronchoconstriction was determined at every visit by a 6-min run with sub-maximal exercise load, on a motor-driven treadmill. FEV1 was measured before running, immediately after and 3, 6, 10, 15 min after running. Maximum percentage falls in FEV1 after exercise was calculated using the formula:  $[(\text{pre-exercise FEV1} - \text{minimum post-exercise FEV1}) \div \text{pre-exercise FEV1}] \times 100$ .

Twenty-five healthy volunteers participated in this study as normal control subjects. None of them had a history of asthma or chronic sinusitis, nor acute upper respiratory infections within the last month.

### **DIAGNOSIS OF ALLERGY**

The intradermal allergen test was employed to determine allergic status. Antigens in this study included house dust, dust mite and inhalant allergens. Total serum IgE levels and serum specific IgE (to dust mite, all the patients of this study showed positive skin test results to dust mite) levels were determined by radioimmunoassay. The reagents for IgE level determination were purchased from Pharmacia Diagnostics (Uppsada, Sweden).

### **SCORES OF CLINICAL SYMPTOMS**

The clinical symptoms of both sinusitis and asthma were scored on a four-point scale: 0 for no symptoms, 1 for mild, 2 for mild severe and 3 for severe. The symptom scores were recorded before and after sinus surgery, as well as at every follow-up visit.

### **TREATMENT OF CRS**

All patients in this group were treated with functional endoscopic sinus surgery. The technique of this surgery is referred to in Kennedy's report.<sup>13</sup> The patients were asked to follow up in the clinic 0.5, 1, 2, 4, 6 and 12 months after the surgical procedure. Necessary treatments were done in the follow-up visits or upon re-admitted into the hospital if required.

### **EVALUATION OF SEB, SPECIFIC ANTIBODIES AND CYTOKINES**

Tissue from surgery was rinsed with PBS and then snap frozen by immersion into liquid nitrogen and stored at  $-70^\circ$

C until use. After weighing, tissue was homogenized with a triple detergent lysis buffer. Following lysis, samples were centrifuged at 12000 rpm for 15 min at 4°C. The BCA assay (Pierce; Rockford, IL, USA) was employed to determine protein concentration of the tissue lysate supernatant. Nasal cavity lavage was done using 5mL saline for each subject. The content of SEB in the tissue lysate and lavage solution was measured using ELISA (Sigma). Total IgE, specific IgE to dust mite and SEB and cytokines including IL-4 and IFN- $\gamma$  were determined with serum samples. Measurement of cytokines was done with enzymatic-linked immunoassay (ELISA, reagents purchased from Sigma, St. Louise, Missouri, USA). Evaluations were done before and after sinus surgery, as well as at every follow-up visit.

**IDENTIFICATION**

Surgical removed tissue was obtained from each patient (a nasal lateral wall swab was obtained from each healthy control instead) that was sent to our Microbiological Laboratory within 30 minutes. The cultures were performed aerobically on blood agar plates. Colonies of different morphology growing on the staphylococcal agar were separately enumerated, subcultured on blood agar, Gram stained, and tested for catalase production. Isolates with a typical Gram-stained appearance and a positive catalase test were tested for coagulase production, and positive isolates were regarded as *S. aureus*. The template DNA was extracted from the positive cultured colony of each subject with the procedures reported by Riffon.<sup>14</sup> PCR was performed with the samples from each subject. The nucleotide sequence is available at the GenBank data library (accession number, X 72700). The primers were designed using the software Primer3 and specificity was tested with Blast. The primers were: 5'- tcaattgcattgctttgct-3' and 5'- gcccttcattttctgcaaa-3'. Amplification was performed on a Perkin-Elmer (Norwalk, Conn.) thermocycler in 25- $\mu$ l reaction mixtures. The program consisted of an initial denaturation step at 94°C for 2 min, followed by 22 cycles of 1 s at 94°C, 2 s at 58°C, and 10 s at 72°C, with a final extension step at 72°C for 5 min. Amplification products were separated on a 1% agarose gel and stained with ethidium bromide before being analyzed on a UV bench by using GelDoc2000 (Bio-Rad).

**STATISTICS**

Data is expressed as means  $\pm$  SD. Statistical significance was determined using the  $t^2$  tests, or ANOVA. Significant difference was accepted when p values were less than 0.05.

**RESULTS**

**INFLAMMATORY TISSUE OF SINUS CONTAINING HIGH CONTENT OF SEB**

Surgically removed tissue and nasal lavage samples were measured for SEB. Healthy control subjects demonstrate a small amount of SEB in their lavage solution (17.7  $\pm$  9.5 pg/ml), whereas patients with rhinosinusitis demonstrated significantly higher levels of SEB in their nasal lavage solution, patients with sinusitis showed much more SEB content in their nasal lavage solution. The surgical removed tissue contained SEB as high as 134.5  $\pm$  47.12 pg/g tissue (Fig 1).

**Figure 1**

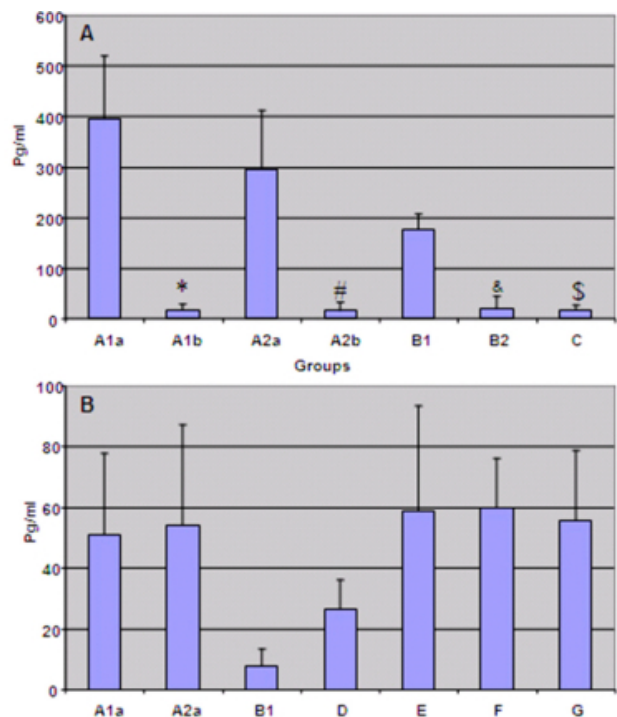
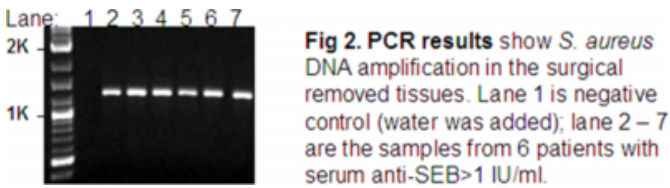


Fig 1. SEB content in sinus (or nasal) lavage fluids (A) and surgical removed tissues (B). Bars stand for SEB content (pg/ml). Groups of patients: A1, patients with serum anti-SEB>1 IU/ml; A2, patients with serum anti-SEB>1 IU/ml and multi-sites infection; B, patients with serum anti-SEB<1 IU/ml; C, healthy controls; D, chronic otitis media; E, chronic dacryocystitis; F, tonsillitis; G, chronic adenoiditis; a, before surgery; b, after surgery.

**SEB WAS IDENTIFIED IN THE SURGICAL REMOVED TISSUE**

*S. aureus* was identified in the surgical removed tissues. All the samples from the patients with serum anti-SEB > 1 IU/ml showed positive results in the culture and further confirmed with PCR (Fig 2). Only 3 (8.8%) samples from the 34 patients with serum anti-SEB < 1 IU/ml showed positive results (p<0.05, compared with those patients with serum anti-SEB > 1 IU/ml). The results also showed positive culture in the samples from 4 (16%) healthy controls.

**Figure 2**



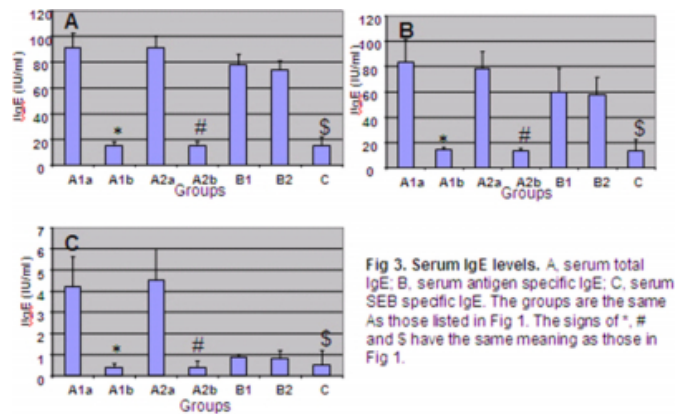
**NASAL POLYPS CORRELATED WITH SERUM ANTI-SEB LEVELS**

Five (5/34, 14.7%) patients had nasal polyps in the group with serum anti-SEB IgE less than 1 IU/ml. 24 (24/51, 47.1%) patients had nasal polyps in the group patient with serum anti-SEB antibody greater than 1 IU/ml ( $p < 0.01$  with  $\chi^2$  test, comparing with the group with anti-SEB less than 1 IU/ml). The group patient with anti-SEB greater than 1 IU/ml was further divided into two sub-groups, sinus infection only group and multi-site infection group. 6 patients had nasal polyps in the patients with multi-sites infection (6/16, 37.5%,  $p < 0.05$ , comparing with the patients with serum anti-SEB less than 1 IU/ml). Of the patients with sinus infection only, 18 patients had nasal polyps (18/35, 51.4%,  $p < 0.01$ , comparing with the patients with multi-sites infection, and the patients with serum anti-SEB less than 1 IU/ml respectively). Correlation analysis was performed with the data of nasal polyp and serum anti-SEB levels. Positive correlation was determined in the patients with serum anti-SEB greater than 1 IU/ml ( $r = 0.63$ ,  $p < 0.01$ , not included the patients with multi-site infections), but not in the patients with serum anti-SEB less than 1 IU/ml ( $r = 0.27$ ,  $p > 0.05$ ). Nasal polyps were radically removed during FESS. No nasal polyps relapsed during the follow-up period.

**SERUM ANTI-SEB ANTIBODY LEVELS DECREASED AFTER SINUS SURGERY**

Upon admittance, serum IgE antibodies including total IgE, antigen specific IgE and anti-SEB antibodies were evaluated. The results are shown in Fig 3. Total IgE and antigen specific IgE antibodies were general higher in the patients of the present study than those healthy controls ( $p < 0.05$ ). SEB-specific antibodies in serum were significantly high in 51 of 85 patients. After sinus surgery, the serum anti-SEB antibody and nasal lavage SEB levels in 35 patients out of the 51 patients decreased significantly and closed to the levels of the normal control subjects.

**Figure 3**



**SERUM CYTOKINE LEVELS WERE AFFECTED BY SINUSITIS**

Before sinus surgery, serum IL-4 was significantly higher; IFN- $\gamma$  levels were significantly lower in all patients with asthma and chronic sinusitis compared with normal controls; after sinus surgery, serum levels of IL-4 significantly decreased and IFN- $\gamma$  level increased in 35 of 85 patients (Fig 5). Correlative analysis showed a positive correlation of anti-SEB antibody with levels of serum IL-4 ( $r = 0.63$ ,  $p < 0.01$ ) and a negative correlation with levels of IFN- $\gamma$  ( $r = -0.76$ ,  $p < 0.01$ ).

Figure 4

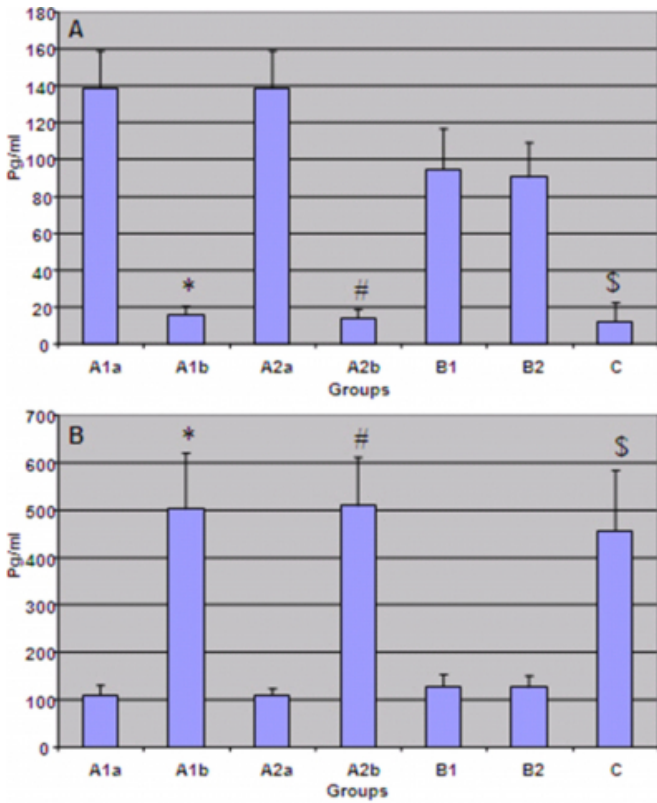


Fig 4. Serum cytokine levels. A, serum IL-4 levels of the patients before and after surgery. B, serum INF- $\gamma$  levels before and after surgery. The groups and significant signs are the same as those in Fig 1.

Figure 5

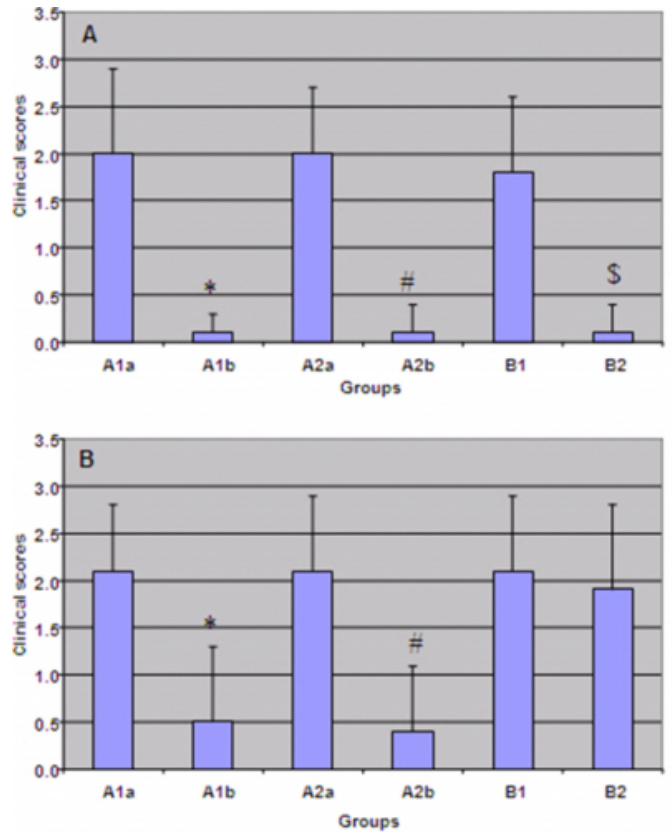


Fig 5. Clinical scores. A, CRS clinical scores. B, asthma clinical scores. The groups and significant signs have the same meaning as those in Fig 1.

### ASTHMA AND SINUSITIS SYMPTOM SCORES IMPROVED AFTER SINUS SURGERY

Nasal blockage and nasal purulent secretions of patients were significantly improved after sinus surgery. Before and after sinus surgery, lung function test data was obtained from all patients. The FEV1 value fall percentage after exercise was not as good as nasal symptom improvement in every patient after sinus surgery. Thirty-five patients who showed improvements in anti-SEB antibody and serum IL-4 and INF- $\gamma$  levels demonstrated significant decreases in asthma symptom scores after sinus surgery ( $p < 0.05$ ); the fall of FEV1 value after exercise in these 35 patients was significantly improved compared with test results obtained before sinus surgery and approaching to the levels of those normal controls. (Fig 6).

**Figure 6**

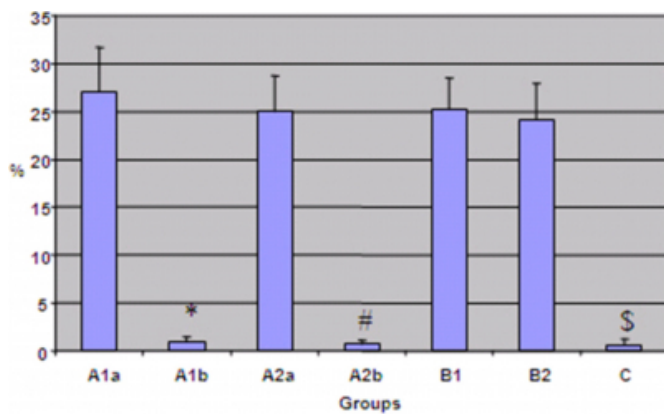


Fig 6. FEV1 fall value before and after surgery. The groups and significant signs have the same meaning as those in Fig 1.

Serum anti-SEB antibody levels of the patients in this study ranged from 0.3 IU/mL to 4.5 IU/mL before sinus surgery. Asthmatic symptom scores correlated with the levels of serum anti-SEB antibody ( $r = 8.12$ ,  $p < 0.01$ ). Patients with serum anti-SEB higher than 1.0 IU/mL before sinus surgery obtained better results of asthmatic symptom relief and pulmonary function improvement than those whose serum anti-SEB was less than 1.0 IU/mL.

### **MULTI-SITES INFECTIONS IN OR AROUND UPPER RESPIRATORY TRACT COULD BE THE REASON THAT SOME PATIENTS' SYMPTOMS WERE NOT IMPROVED AFTER SINUS SURGERY**

Fifty (58.82%) patients did not obtain satisfactory improvement in their asthma one month after sinus surgery. Three of these perceived their asthma to be worse after surgery. A review of these case files was done, we found that 5 patients had chronic tonsillitis, 6 patients had residual adenoiditis, 2 patients had chronic otitis media, and 3 patients had dacryocystitis. These 16 patients with additional infections showed high levels of serum anti-SEB, IL-4 and low levels of IFN- $\gamma$  before sinus surgery and neither showed little effect on decreasing anti-SEB antibodies, serum IL-4 and IFN- $\gamma$  levels and almost no improvement on their clinical asthma symptoms although the sinusitis clinical symptoms were significantly improved following sinus surgery.

All of these 16 patients underwent surgical treatments for these disorders within two months after the sinus surgery, with subsequent improvement in their asthmatic symptoms. These patients no longer require any anti-asthma medications. Laboratory results showed decreased serum anti-SEB antibodies, IL-4, with increased IFN- $\gamma$  levels

compared with the data before surgery ( $p < 0.01$ ), with values approaching those of normal controls ( $p > 0.05$ ). SEB was also evaluated with these surgically removed tissues.

The remaining 34 patients showed little or no improvement in their asthmatic symptom scores and continued needing to use anti-asthma medications sometimes or regularly. Laboratory results showed they had low levels serum anti-SEB antibody levels that were close to the normal control values ( $p > 0.05$ ) and much less than the anti-SEB antibody levels (before sinus surgery) of the patients who achieved satisfactory results after sinus surgery.

### **DISCUSSION**

These results provide evidence that the improvement of asthmatic symptoms and pulmonary function by sinus surgery in patients with both asthma and sinusitis correlate with the alteration of some special antibodies and cytokines. Since the asthma symptoms occurred after sinusitis, and disappeared after sinusitis treatment, it implicates a close relationship between these two disorders. To our knowledge, this is the first report which indicates that bacteria superantigen SEB plays a crucial role in the low airway hypersensitivity related to chronic sinusitis. There have been some reports about the effects of sinus surgery on the relief of asthma symptoms. McFadden<sup>15</sup> observed a group of patients with sinusitis and asthma undergoing sinus surgery and showed subjective improvement and increased respiratory function; sixty-eight patients (85%) had significant improvement in their sinus symptoms and 67 (83%) had relief of their asthma. Jankowski<sup>16</sup> reported on 30 patients and 91% showed asthma improvement. In the present study, the results approximate to those reports we mentioned above, the first follow-up visit one month after the sinus surgery showed that only 41.18% patients had satisfactory asthmatic symptom relief. The rest, 58.12% of patients still had asthma symptoms, required medical management, and 3 patients were even worse than that before sinus surgery. However, the novel finding of this study is that further investigation of these subjects revealed that they suffered from more than one site of chronic infection in the upper respiratory tract or surrounding area. After relieving these disorders, these 16 patients had improved results in controlling the asthmatic symptoms. In summary, the present data showed a satisfied rate of patients resolved their sinusitis problem and 60% patients resolved their asthmatic symptoms with sinus surgery. The results and the supporting literature suggest that sinusitis might induce

low airway hypersensitivity under certain conditions.

*Staphylococcus aureus* is a representative constituent of bacterial flora in the nasal cavity and a common pathogen, although various results have been reported.<sup>5</sup> *S. aureus* produces a set of proteins (SEA, SEB, TSST-1), which act both as superantigens and toxins. The present results show that a certain quantity of SEB in the lavage solution of nasal cavity and in the surgically removed tissue, and anti-SEB antibody in the serum presents in most patients with sinusitis and normal control subjects. The data provide evidence that a large proportion of patients in this study suffered from *S. aureus* infection of sinus. These *S. aureus* colonize in the sinus and produce SEB. SEB has potent immune manipulative capability. It can activate T cells without assistance of antigen processing cells, so as to initiate immune reactions. Herz, et al<sup>18</sup> reported murine airway inflammation was triggered only by superantigen exposure in dose-dependent manner that was characterized by mucosal and airway recruitment of lymphocytes, eosinophils and neutrophils together with elevated levels of IL-4 but not IFN- $\gamma$ , in bronchoalveolar lavage fluids. The present results showed high SEB levels present in the nasal cavity of patients with chronic sinusitis before sinus surgery that were significantly decreased after sinus surgery. It indicates that SEB arises from the inflammatory sinuses, and also raises a question of whether the SEB produced by chronic sinusitis also affects the lower respiratory tract and if so, how? The clinical results of the present study showed significant improvement of asthmatic symptoms after resolving sinus disorders and thus provide supporting evidence for this hypothesis. Since we did not use any asthma medication for the patients in the present study, resulting asthma relief are logically considered as an effect of the sinus surgery. This is consistent with many other reports regarding this topic.<sup>18, 19</sup>

Th2 cytokines such as IL-4 play crucial roles in airway hypersensitivity.<sup>20</sup> Consistent with previous reports, the present data also showed significantly increased serum IL-4 of the patients, as well as lower serum IFN- $\gamma$  level compared to normal controls before the treatment of sinusitis. IL-4 is the predominant cytokine produced by Th2 CD4+ lymphocytes and is important for isotype switching to IgE and IgG4. IL-4 is also the most potent up-regulator of CD23 antigen, the low-affinity IgE receptor.<sup>21</sup> CD23 has the potential to facilitate extrinsic antigens to be transported across the epithelial barrier.<sup>22</sup> This group of patients also showed increases in serum antigen specific IgE, with

positive intradermal antigen test results. These data demonstrate the hypersensitivity status of these patients. The interesting results in this study are these cytokines, IgE antibody as well as their clinical symptoms showed a tendency towards normal levels in 60% patients after sinus surgery. A possible explanation for these data might be that after we cleaned the pathogen from the sinuses, we removed the major pathogenic stimulus (SEB) from the airway mucosa. With lack of stimulation, the increased permeability of the airway epithelial barrier recovered<sup>6</sup> and re-established the capability in preventing antigens from being transported across the airway epithelial barrier. Once the extrinsic stimuli are removed, the previously unbalanced immune functions recover by self-regulating mechanisms.

The results showed that relief of asthmatic symptoms correlated with increased SEB levels in the nasal cavity, as well as anti-SEB antibodies in the serum. It indicates that only a part of the patients with chronic sinusitis has *S. aureus* infection, the fact is also reported by other investigators.<sup>23</sup> It also emphasizes the significance of the concept that relief of asthma by sinus surgery in the patients with both sinusitis and asthma is relevant to the patients infected by *S. aureus*. It is true that a proportion of patients in this study with high levels of serum SEB antibody did not achieve good clinical outcome for their asthma after sinus surgery, but further investigation revealed that these patients also suffered from *S. aureus* infection in other organs around or in the upper respiratory tract in addition to sinusitis. We also detected high levels of SEB in surgically removed tissues were possible sources of SEB that affect the lower respiratory tract. Other investigators also reported *S. aureus* infection in these organs. Brook<sup>24</sup> reported *S. aureus* in the inflammatory adenoids and otitis media while Izaki<sup>25</sup> reported staphylococcal infection in the oral cavity in a group of the patients with chronic tonsillitis. Our data in this portion of patients further confirms the significance of *S. aureus* infection in the upper respiratory tract on inflammation of lower respiratory tract.

## CORRESPONDENCE TO

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