

Change in Serum IgE Levels Following Surgery in Patients with Allergic Fungal Rhinosinusitis is Predictive of Disease Status

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Abstract

Objective: We aimed to correlate post-operative endoscopic disease status and reduction in serum total IgE levels in patients with allergic fungal rhinosinusitis (AFRS) and to ascertain whether this reduction has prognostic significance.

Material and Methods: A prospective cohort of 50 patients with biopsy-proven AFRS underwent preoperative endoscopy and serum total IgE assessment. Following endoscopic excision of polyps and allergic mucin and post-operative steroid therapy, patients were re-evaluated at 3-6 months with nasal endoscopy with Kupferberg staging and serum total IgE levels.

Results: There were 27 (54%) male and 23 (46%) female patients. Preoperative endoscopy showed grade 3 polyps in 33 (66%) patients and grade 2 polyps in 17 (34%) patients. Post-operatively, 37 (74%) patients had Stage 0, 11 (22%) had Stage 1, and two (4%) had Stage 2 diseases. Preoperative IgE levels ranged from 153.2 to 6,548.2 IU mL⁻¹. Post-operative IgE levels were reduced in 42 of 50 (84%) patients and ranged from 79.9 to 3,900 IU mL⁻¹. There was a negative correlation between percentage change in IgE and post-operative endoscopic score, which was significant ($r = 0.25$; $P = .032$). Based on receiver operating characteristic analysis, a percentage reduction in IgE of $\geq 32\%$ had a sensitivity of 69.2% (95% CI: 38.6-90.9) and specificity of 67.6% (95% CI: 50.2-82.0) in predicting endoscopic stage.

Conclusion: Post-operative reduction in serum total IgE levels negatively correlates with endoscopic stage in AFRS patients who undergo surgery and post-operative steroid therapy. A cutoff of $\geq 32\%$ in change in IgE levels is predictive of endoscopic Stage 0 disease.

Keywords: Immunoglobulin E, rhinosinusitis, fungal allergy, chronic rhinosinusitis with nasal polyps

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INTRODUCTION

Allergic fungal rhinosinusitis (AFRS) is a type of noninvasive fungal sinusitis whose diagnosis is based on several well-defined criteria.¹ The fungal species associated with the disease are *Aspergillus* species and dematiaceous fungi. In the Indian subcontinent, *Aspergillus* is the major species encountered.² One of the unique features seen in patients with AFRS is allergic mucin, a gelatinous substance with a "peanut butter" like appearance and distinct histological features.¹

An IgE-mediated allergic pathogenesis has been proposed for AFRS.^{1,3} Studies have shown that both total serum IgE levels and fungal specific IgE levels are often elevated in the disease.^{1,3-6} The rise in IgE levels is an indication of dysregulation of the immune system in the presence of allergy. Some patients have been reported to have a rise in local IgE levels.⁷

The current treatment protocol for allergic fungal sinusitis is endoscopic excision of polypoid mucosa and allergic mucin with provision of wide drainage of the sinuses and retention of normal mucosa. Post-operative oral steroid is recommended to prevent recurrence of disease.⁸ Intranasal corticosteroids or topical steroid nasal washes are also administered simultaneously and continued for several months to years. Post-operative assessment of disease is best performed by endoscopy using the Kupferberg endoscopic scale,⁴ which has four stages starting from Stage 0.

Recurrence following the preliminary surgery and post-operative steroid therapy is well known, and recurrence rates range from 10 to 100%.⁹

Following surgery and steroid therapy, IgE levels will show a fall in most patients with AFRS.³ The association between this reduction in IgE levels and endoscopic evidence of disease in patients on follow-up has been less well studied. Kupferberg et al.⁴ suggested that serial total and specific IgE levels may be useful in assessing the success of therapy. If such an association is found, it would help to avoid unnecessary radiological studies to assess the presence of disease, particularly if endoscopic appearances are equivocal or a complete endoscopic assessment is difficult to perform or unacceptable to the patient. The present study, therefore, aims to study the correlation between post-operative endoscopic appearance and reduction in serum total IgE levels in patients with AFRS and analyze whether this reduction has prognostic significance.

METHODS

A prospective observational study was conducted among 50 patients who were diagnosed with AFRS based on standard Bent and Kuhn's¹ criteria and underwent surgery and medical management of their disease. Patients less than 18 years of age and those with other coincident sino-nasal disease were excluded from the study.

Preoperative Assessment

After obtaining an informed consent, data regarding demography, comorbidities, symptoms, endoscopic grading of polyps, radiological features, skin allergy testing results, fungal culture results, and preoperative IgE levels were collected. Radiological evaluation of the CT scan was done using Lund and Mackay grading system.

Preoperative grading of nasal polyps was performed as follows:

- Grade 1: Polyp confined to the middle meatus
- Grade 2: Polyps projecting just beyond the middle meatus
- Grade 3: Polyps completely filling the nasal cavity

Post-operative Assessment

All patients were followed-up after 3-6 months and longer (wherever possible), and repeat rigid nasal endoscopy and serum total IgE level testing were performed. Post-operative staging of disease was performed as per the Kupferberg staging system,⁴ which was as follows:

- Stage 1: No evidence of disease
- Stage 1: Edema of mucosa; no allergic mucin
- Stage 2: Polypoid change with no allergic mucin
- Stage 3: Polyps and allergic mucin

Surgical Management

All patients underwent endoscopic sinus surgery commensurate with the extent of disease. The ostia were widely opened out, and all polypoid tissue and fungal debris thoroughly excised. There was a liberal use of saline washes to remove every bit of fungal debris.

Medical Management

All patients were commenced on oral steroid therapy at a dose of 1 mg kg⁻¹ day⁻¹ for 5 days from the day of surgery followed by 0.5 mg kg⁻¹ day⁻¹ for another 5 days. Post-operatively, they also received budesonide nasal irrigation twice a day and plain saline washes four times a day for 3 weeks, followed by budesonide nasal irrigation alone twice daily for 3 months. Budesonide irrigation was prepared by mixing one pack of 0.5 mg/2 mL commercially available budesonide respules (Derinide; Zydus Cadila) with a 250 mL normal saline in a squeeze bottle. Half of the solution was used for each nasal cavity. At the first post-operative visit between 3 and 6 months following surgery, if they had stage 0 disease,

Table 1. Distribution of Symptoms in Patients with AFRS (n = 50)

Symptom	Number (%)
Nasal obstruction	50 (100)
Nasal discharge	49 (98)
Sneezing	32 (64)
Headache	17 (34)
Post nasal drip	6 (12)
Facial pain	4 (8)
Visual disturbance	3 (6)
Epiphora	3 (6)
Proptosis	2 (4)
Anosmia	1 (2)
Visual disturbances	1 (2)

they were asked to use a steroid nasal spray at a dose of two sprays at night and twice daily saline sprays until the next check-up a year later.

Statistical Analysis

Frequencies and percentages of categorical variables and means with standard deviation of continuous variables were calculated. Change in IgE levels at follow-up was calculated as a percentage of the preoperative level by using the formula: (preoperative IgE level – follow-up IgE level)/ (preoperative IgE level) × 100. Correlation between post-operative endoscopic score and percentage change in IgE levels was calculated using Kendall's tau B test. A receiver operating characteristic (ROC) curve in which sensitivity is plotted against (1-specificity) for different % change of IgE level cutoffs was drawn to determine the best cutoff for predicting stage 0 disease. We also studied the correlation between the preoperative IgE level and the percentage post-operative reduction in IgE levels using Spearman rank correlation. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 16.0 (IBM SPSS Corp.; Armonk, NY, USA).

RESULTS

Demography

There were 27 (54%) male and 23 (46%) female patients. Patients' ages ranged from 21 to 60 years, with a mean of 38.62 ± 11.21 years. The predominant symptoms at presentation were nasal obstruction (100%), nasal discharge (98%), sneezing (64%), and headache (34%) (Table 1). Common comorbidities seen were hypertension (22%), diabetes mellitus (6%), and bronchial asthma (2%). Sixteen (32%) patients had undergone prior sinus surgery.

Mycology

Fungal smear testing revealed septate fungal hyphae in all patients. Fungal culture showed *Aspergillus* species in 50%, *A. flavus* in 26%, *A. fumigatus* in 4%, a combination of *A. fumigatus* and *A. flavus* in 2%, and *Curvularia* species in 2%. Fungal cultures were negative in 16% of patients.

Skin Allergy Testing

Skin allergy testing results showed dust mite allergy in most patients with 89.1% allergic to *Dermatophagoides farinae* and 68.9% to

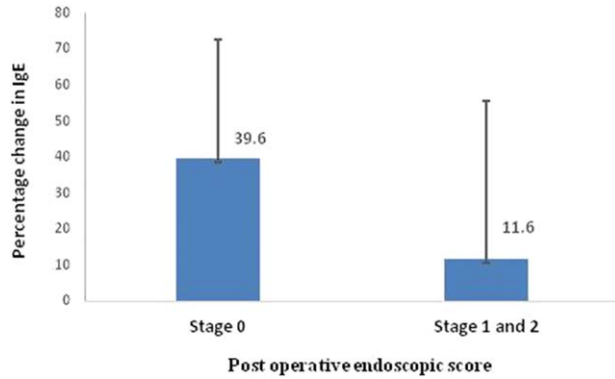


Figure 1. Error bar showing mean percentage change in IgE for post-operative endoscopic scores of Stage 0 and Stages 1 and 2.

Dermatophagoides pteronnysinus. Reactivity to one or more fungal allergens like *A. fumigatus*, *A. flavus*, *Alternaria alternata*, *Curvularia lunata*, *Fusarium sp.*, and *Candida sp.* was seen in 67.4%.

Preoperative Rigid Nasal Endoscopy

Preoperative rigid nasal endoscopy showed grade 3 polyps in 33 (66%) patients and grade 2 polyps in 17 (34%) patients.

Radiology

CT scan of the paranasal sinuses showed opacification of the affected sinuses with hyperdense areas in all patients. Mean Lund-Mackay scores were 9.50 ± 3.68 (IQR = 11.50 (8.0, 12.0)) on the right side and 8.70 ± 3.87 (IQR = 10.50 (5.0, 12.0)) on the left side. Bone erosions were seen in 16 (32.7%) patients, intraorbital involvement in 6 (12%) patients, and intracranial involvement in 3 (6%) patients.

Preoperative Serum Total IgE Levels

Preoperative serum total IgE levels ranged from 153.2 to 6,548.2 IU mL⁻¹ (IQR = 1,178.90, 2,588.02) with a mean of $1,882.46 \pm 1,245.79$ IU mL⁻¹ and median of 1,531.70 IU mL⁻¹.

Follow-Up Evaluation

Duration of follow-up after surgery ranged from 3 to 6 months (mean = 4.3 months). Post-operative IgE levels ranged from 79.9 to 3,900 IU mL⁻¹ (IQR = 427.15, 1,818.73), with a mean of $1,466.26 \pm 2,184.89$ IU mL⁻¹ and median of 856.45 IU mL⁻¹.

Post-operative endoscopic score showed Stage 0 disease in 37 (74%) patients, Stage 1 disease in 11 (22%) patients, and Stage 2 disease in two (4%) patients.

Change in IgE Levels Post-Operatively

Most (86%) patients showed a reduction in IgE levels at follow-up. In eight patients, there was a rise in IgE values at follow-up. Four patients with Stage 0 disease had increase in IgE values ranging from 3.8 to 486.3, and four patients with Stage 1 disease had post-operative rise in IgE values that ranged from 18.4 to 703.3. The mean percentage change in IgE levels was 39.6% for those patients who achieved Stage 0 and 11.6% for those who achieved Stages 1 or 2 post-operatively (Figure 1).

Correlation between Preoperative IgE Levels and Percentage Change in Post-Operative IgE Levels

No correlation was seen between preoperative IgE and post-operative IgE percentage change (Spearman rank correlation $r = 0.076$, $P = .634$) (Figure 2).

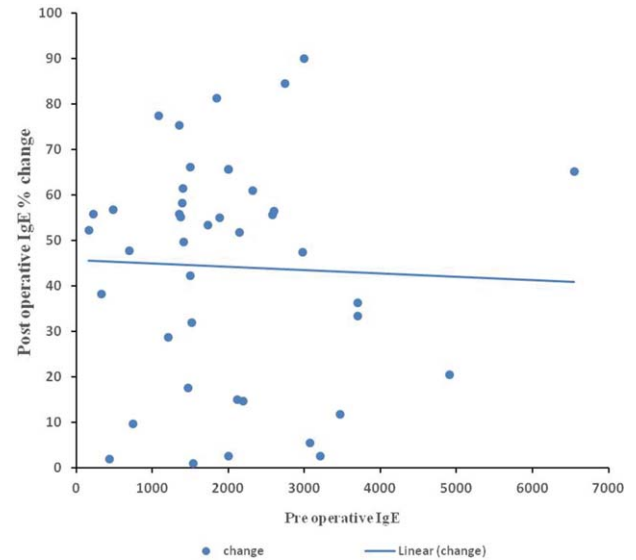


Figure 2. Scatter plot showing lack of correlation between preoperative total IgE levels and percentage change in post-operative IgE levels (Spearman rank correlation $r = -0.076$; $P = .634$).

Correlation between Percentage Change in Post-Operative IgE Levels and Post-Operative Endoscopic Score

There was a negative correlation between percentage change in IgE and post-operative endoscopic score. Kendall's tau correlation coefficient was 0.25. This was significant ($P = .032$) (Figure 3).

ROC Analysis

For the percentage change in IgE based on the Youden index associated criterion, the best threshold was found to be $\geq 32\%$ change with a sensitivity of 67.6% (95%CI: 50.2-82.0) and a specificity of 69.2% (95% CI: 38.6-90.9) (Figure 4).

DISCUSSION

The results of this study show that post-operative fall in total serum IgE levels may indeed be a useful surrogate marker for the absence of

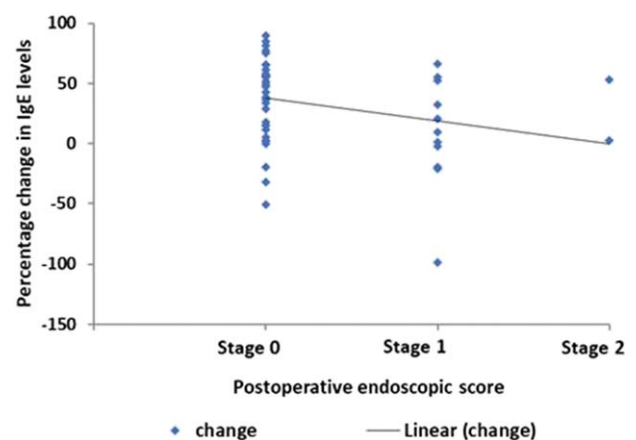


Figure 3. Scatter plot showing negative correlation between percentage change in post-operative IgE levels and post-operative endoscopic score ($r = 0.25$; $P = .032$).

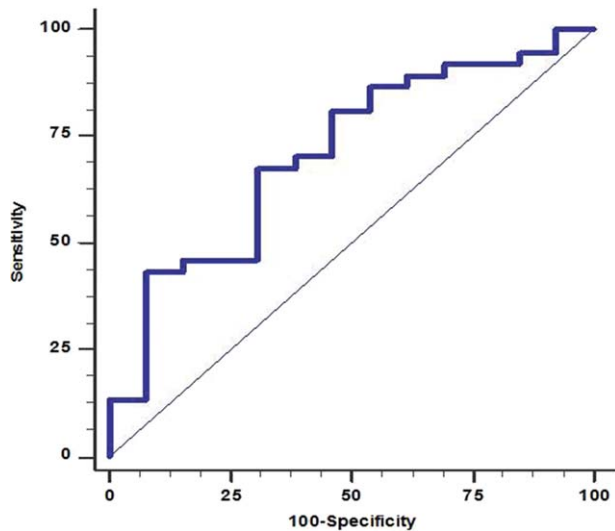


Figure 4. ROC curve for percentage change in IgE levels and post-operative endoscopic score.

disease in patients who have undergone treatment for AFRS. There appears to be a significant negative correlation ($r = 0.25$; $P = .032$) between a percentage fall in total serum IgE levels and endoscopic score. Thus, a patient with Stage 0 endoscopic score may be expected to have significant reduction in post-operative IgE levels (Figure 3). Changes in IgE levels along with rigid nasal endoscopy on longitudinal follow-up are the ideal parameters to be monitored in the majority of patients. The results of our study show that a fall in IgE of $\geq 32\%$ correlated with Stage 0 disease and knowledge of this cutoff is likely to be of use in prognosticating outcomes following therapy.

A raised total serum IgE level is not by itself a diagnostic criterion of AFRS. In our study, all patients had a raised preoperative total serum IgE level (normal value $< 85 \text{ U mL}^{-1}$). Bent and Kuhn¹ found that six out of seven (85.7%) patients had raised IgE levels in patients with AFRS, while Marple¹⁰ found a rise in only four out of 17 (23.5%) patients. Manning et al.,³ in contrast, found that 15 out of 16 patients (93.8%) had raised total serum IgE levels. Despite AFRS being an IgE-mediated disease, elevation of total serum IgE levels is not universally seen. Unlike allergic bronchopulmonary aspergillosis where a cutoff of $1,000 \text{ IU mL}^{-1}$ is given as a diagnostic criterion,¹¹ in AFRS (although the Bent and Kuhn criteria for diagnosis refer to type 1 hypersensitivity as being an important criterion), there is no IgE cutoff that is diagnostic.¹ In some patients, it may be local rather than systemic IgE level that is raised.⁷ Locally, produced IgE may also be the reason for some patients showing no systemic evidence of allergy despite having all the features of AFRS.⁷

Post-operative reduction in serum IgE is probably related to the reduction in burden of IgE-mediated allergic mucin following the surgical removal as well as the anti-inflammatory effect of steroid therapy. In our study, we found reduction of total serum IgE levels in the post-operative period in 84% of patients. In eight (16%) cases, total serum IgE levels were not reduced despite clinical and endoscopic improvement with four (8%) of these patients having Stage 0 and the other four (8%) having Stage 1 scores. This may be because of a strong immunological response which may require a longer duration of oral steroid therapy to reduce IgE levels to less than the preoperative levels.

Does the percentage reduction in IgE depend on the preoperative IgE level? Some authors suggest that preoperative IgE levels may be used to screen for advanced AFRS in patients with chronic rhinosinusitis with nasal polyposis.⁶ The results of our study showed, however, that there is no such relationship, even though preoperative IgE levels are often quite high in AFRS.

In conclusion, a reduction in post-operative serum total IgE correlates well with Kupferberg endoscopic score and may serve as a surrogate marker of disease presence in patients with AFRS on follow-up. A cutoff of $\geq 32\%$ of reduction in preoperative IgE levels appears to show the best correlation with Stage 0 disease.

Ethics Committee Approval: Ethical committee approval was received from the Institutional Review Board and Ethics Committee of Christian Medical College, Vellore. (IRB No. 10893).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Resources - N.J.; Materials - N.J.; Data Collection and/or Processing - N.J., T.M.; Analysis and/or Interpretation - N.J., T.M.; Literature Search - N.J., T.M.; Writing Manuscript - N.J., T.M.; Critical Review - N.J., T.M.

Conflict of Interest: The authors have no conflicts of interest to declare.

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