

Gender-specific differences in serum immunoglobulin E levels and prevalence of fungus in sinonasal tissue noted in patients with chronic rhinosinusitis who underwent endoscopic sinus surgery

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ABSTRACT

Background: We previously presented that women with chronic rhinosinusitis (CRS) who elected endoscopic sinus surgery (ESS) have a higher symptom burden than men. Causes of these gender-based differences warranted further study.

Objectives: To study gender differences in another cohort of adult patients with CRS who underwent ESS and to compare key histopathologic and serologic features

Methods: Patients with CRS who underwent ESS (from 2011 to 2014) with structured histopathology reports on surgical samples were studied. The 13-item structured histopathology report detailed key metrics of inflammation and the presence of fungal elements. Clinical, 22-item Sino-Nasal Outcome Test (SNOT-22) score, Lund-Mackay computed tomography (CT) score, serologic (immunoglobulin E [IgE] level, absolute eosinophil count) and histopathologic data were compared between male and female patients by using statistical software.

Results: We studied 130 eligible subjects (mean age, 54.7 years; 49.2% women). Compared with the men, the women had significantly higher preoperative SNOT-22 scores (women, 48.7; men 38.0 [$p = 0.004$]) but similar CT scores. Serum IgE levels were significantly higher among women versus men (peak, 433.3 versus 190.8 kU/L [$p = 0.03$]; closest to surgery, 435.0 versus 190.8 kU/L [$p = 0.03$]). Tissue fungal elements were significantly more prevalent in women versus men (19.0 versus 5.2%; $p = 0.02$). Up to this point, the analysis was agnostic of clinical details of the subjects. Further analysis was conducted regarding clinical features. Allergic fungal sinusitis (AFS) was found significantly more commonly in the female versus male patients (21.9 versus 9.1%; $p = 0.04$). Women versus men had a higher prevalence of migraine (19.4 versus 4.6%; $p = 0.01$) or any primary headache disorders (23.0 versus 6.2%; $p = 0.007$).

Conclusion: Women who underwent ESS for CRS had higher SNOT-22 symptom burden. Worsened symptomatology may be secondary to a higher prevalence of primary headache disorders in women. However, surgeons should also be aware that female patients with CRS who seek ESS may have a higher prevalence of severe disease endotypes (more tissue fungal elements, elevated serum IgE levels) and phenotypes.

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Chronic rhinosinusitis (CRS) is one of the most commonly prevalent conditions in the United States.¹ CRS can cause major impairment to quality of life^{1,2} and affects women more often than men.^{1,3,4} Women also report significantly higher symptom burden from CRS.^{3–5} In previous studies, we used the 22-item Sino-Nasal Outcome Test (SNOT-22)⁶ quality-of-life questionnaire to compare CRS symptom severity between female and male subjects with CRS.^{3,4} We found that women experienced a higher subjective burden of disease as measured by the total SNOT-22 score, despite having a similar or lower objective burden as evaluated by an objective sinus computed tomography (CT) score (total Lund-Mackay CT score).^{3,4,7} In addition, although endoscopic sinus surgery (ESS) results in a similar and significant magnitude of improvement in both genders,

postoperative total SNOT-22 scores remain significantly worse in women.⁴

In a gender-based analysis of patients with CRS, Mendolia-Loffredo *et al.*⁵ reported a higher symptom burden in women. They ascribed worsened symptomatology in women to the higher prevalence of aspirin-exacerbated respiratory disease (AERD) and depression in women.⁵ In our previous study, we identified a higher prevalence of comorbid primary headache disorders in women but could not validate a higher prevalence of anxiety, depression, or AERD in women.⁴ The causes of a higher symptom burden in women prompted us to look at objective metrics of inflammation associated with CRS beyond the sinus CT disease burden (which is lower or equivalent in women^{3,4}), particularly because the disease seems to preferentially afflict women.

Despite recent advancements in research on CRS, the pathogenesis of this widespread condition and its etiologies remain poorly understood,^{1,8–10} and this impacts our understanding of gender-based differences. Many disease-modifying factors have been identified, and mucosal tissue obtained from patients with CRS who undergo ESS exhibit an array of inflammatory markers and inflammatory patterns.⁸ Furthermore, serum markers of inflammation, *e.g.*, immunoglobulin E (IgE), have also been found to modify disease severity.^{11,12} Given this histopathologic heterogeneity in disease spectrum, as well as the impact of serum inflammatory markers on disease severity, we set out to explore gender differences in well-described histopathologic and serologic markers of CRS.

METHODS

The study was conducted at the Mayo Clinic in Arizona and was approved by the institutional review board of the Mayo Clinic. A

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Table 1 Clinical characteristics of the study cohort

Clinical Characteristics	Women (n = 64)	Men (n = 66)	Total (N = 130)	p Value
Age at surgery, mean $\pm$ standard deviation	52.4 $\pm$ 15.9	56.9 $\pm$ 14.8	54.7 $\pm$ 15.5	0.10
Chronic rhinosinusitis with nasal polyposis, no. (%)	31 (48.4)	34 (53.1)	65 (50.8)	0.6
Allergic fungal sinusitis, no. (%)	14 (21.9)	6 (9.1)	20 (15.4)	0.04
Aspirin exacerbated respiratory disease, no. (%)	11 (19.6)	6 (10.5)	17 (15.0)	0.20
Asthma, no. (%)	30 (50.0)	31 (47.7)	61 (48.8)	0.8
Depression, no. (%)	7 (11.1)	9 (13.6)	16 (12.4)	0.66
Anxiety, no. (%)	8 (12.7)	5 (7.7)	13 (10.2)	0.35
Migraine, no. (%)	12 (19.4)	3 (4.6)	15 (11.8)	0.01
Any primary headache disorder, no. (%)	14 (23.0)	4 (6.2)	18 (14.3)	0.007

Table 2 Details of Preop and postop SNOT-22 scores of the study subjects

	SNOT-22 Score				Change in SNOT-22 Score from Baseline			
	Women (n = 64)	Men (n = 66)	Total (N = 130)	p Value	Women (n = 64)	Men (n = 66)	Total (N = 130)	p Value
Baseline (preop)								
No.	63	66	129					
Mean $\pm$ SD	48.7 $\pm$ 20.9	38.0 $\pm$ 20.2	43.3 $\pm$ 21.2	0.004				
3 Months postop								
No.	59	59	118		58	59	117	
Mean $\pm$ SD	17.7 $\pm$ 15.9	13.1 $\pm$ 12.9	15.4 $\pm$ 14.6	0.09	-33.2 $\pm$ 20.2	-25.0 $\pm$ 18.1	-29.0 $\pm$ 19.5	0.02
6 Months postop								
No.	39	37	76		39	37	76	
Mean $\pm$ SD	20.3 $\pm$ 16.3	11.5 $\pm$ 11.6	16.0 $\pm$ 14.8	0.008	-28.1 $\pm$ 19.9	-23.8 $\pm$ 16.8	-26.0 $\pm$ 18.5	0.31
12 Months postop								
No.	21	22	43		21	22	43	
Mean $\pm$ SD	26.6 $\pm$ 22.7	17.5 $\pm$ 15.5	21.9 $\pm$ 19.7	0.14	-24.5 $\pm$ 20.1	-20.8 $\pm$ 18.4	-22.6 $\pm$ 19.1	0.53
24 months postop								
No.	12	16	28		12	16	28	
Mean $\pm$ SD	20.8 $\pm$ 18.5	20.4 $\pm$ 19.1	20.6 $\pm$ 18.5	0.97	-35.0 $\pm$ 22.2	-15.9 $\pm$ 17.1	-24.1 $\pm$ 21.3	0.02

Preop = Preoperative; postop = postoperative; SNOT-22 = 22-item Sino-Nasal Outcome Test; SD = standard deviation.

cross-sectional analysis of adult patients with CRS who underwent ESS from 2011 to 2014 was studied. Patients with acute sinusitis, recurrent acute sinusitis, and invasive fungal sinusitis, and those who underwent surgery exclusively for nasal obstruction were excluded. Patients who had sinonasal surgical mucosal tissue analyzed with a detailed and structured histopathology report, as described by Snidvongs *et al.*,¹³ were chosen for further study. The electronic medical records were reviewed to collect information on basic demographics, clinical presentation, a diagnosis of CRS subtype (CRS with polyps [CRSwNP] or CRS without polyps), SNOT-22 scores, Lund-Mackay CT scores, and standardized histopathology reports. Serum IgE and eosinophil levels (peak levels and the level closest to the time of surgery) were also studied; These two systemic markers were chosen because they have been noted to be associated with more severe forms of CRS^{1,2} and were also commonly tested in our clinic. For both of those measurements, we accounted for the closest available value to the date of surgery as well as the highest recorded value available for each patient.

The standardized surgical histopathologic report was generated by a group of dedicated head and neck pathologists.¹³ The metrics reported and compared were the following: the overall degree of inflammation (mild, moderate, or severe), eosinophil count per high power field, basement membrane thickness ($\leq$ or $>15 \mu\text{m}$), predominant inflammatory background (*e.g.*, eosinophilic, neutrophilic, lymphocytic) and the presence or absence of the following: neutrophilic infiltration, subepithelial edema, hyperplastic and/or papillary change, mucosal ulceration, squamous metaplasia, fibrosis, fungal elements, Charcot-Leyden crystals, and eosinophil aggregates. Total

SNOT-22 scores were collected. The SNOT-22 scoring system is a quality-of-life questionnaire with 22 items that question patients on rhinologic, nonrhinologic-otolaryngic, psychological, and sleep functions. Each question is graded on a 6-point scale based on severity, for a maximum score of 110 points.⁶ The burden of CRS on a CT was estimated by using the Lund-Mackay scoring system. The total score ranged from zero (no disease) to a maximum of 24 (complete opacification of all paranasal sinuses and ostiomeatal complex).⁷

Statistical Analysis

Demographics, SNOT-22 scores, Lund-Mackay scores, histopathology reports, and the aforementioned laboratory results were analyzed and compared between the male and female subjects. Categorical data were reported as frequency count and percentage, and the comparison between the male and female patients was performed by using the χ^2 test. Continuous data were reported as mean $\pm$ standard deviation and median, and were compared with the use of the two-sample *t*-test (or Wilcoxon rank sum test if applicable). All these tests were two-sided, and a *p* value of <0.05 was considered statistically significant. The analyses were conducted by using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Demographic and Background Information

Demographic and background information are presented in Table 1. A total of 340 patients with CRS underwent ESS during the study

Table 3 Comparison of tissue histopathology report between the men and women in the study

	Women, no. (%) (n = 64)	Men, no. (%) (n = 66)	Total, no. (%) (N = 130)	p Value
Overall degree of inflammation				0.16
Mild	20 (31.3)	30 (46.2)	50 (38.8)	
Moderate	36 (56.3)	26 (40.0)	62 (48.1)	
Severe	8 (12.5)	9 (13.9)	17 (13.2)	
Eosinophil count				0.71
≤10 per hpf	28 (43.8)	31 (47.0)	59 (45.4)	
>10 per hpf	36 (56.3)	35 (53.0)	71 (54.6)	
Neutrophilic infiltrate				0.11
Absent	35 (55.6)	45 (69.2)	80 (62.5)	
Present	28 (44.4)	20 (30.8)	48 (37.5)	
Inflammatory predominance				
Lymphocytic	16 (25.0)	18 (27.3)	34 (26.2)	0.77
Lymphoplasmacytic	36 (56.3)	31 (47.0)	67 (51.5)	0.29
Eosinophilic	25 (39.1)	19 (28.8)	44 (33.8)	0.22
Lymphohistiocytic	0 (0.0)	1 (1.5)	1 (0.8)	0.32
Neutrophilic	2 (3.1)	1 (1.5)	3 (2.3)	0.54
Other	0 (0.0)	2 (3.0)	2 (1.5)	0.16
Basement membrane thickening				0.18
Absent	5 (7.8)	12 (18.2)	17 (13.1)	
≤15 μm	35 (54.7)	29 (43.9)	64 (49.2)	
>15 μm	24 (37.5)	25 (37.9)	49 (37.7)	
Subepithelial edema				0.45
Absent	14 (22.2)	11 (16.9)	25 (19.5)	
Present	49 (77.8)	54 (83.1)	103 (80.5)	
Hyperplastic and/or papillary change				0.95
Absent	57 (89.1)	59 (89.4)	116 (89.2)	
Present	7 (10.9)	7 (10.6)	14 (10.8)	
Mucosal ulceration				0.96
Absent	58 (90.6)	60 (90.9)	118 (90.8)	
Present (with reactive changes)	6 (9.4)	6 (9.1)	12 (9.2)	
Squamous metaplasia				0.83
Absent	57 (90.5)	59 (89.4)	116 (89.9)	
Present	6 (9.5)	7 (10.6)	13 (10.1)	
Fibrosis				0.89
Absent	12 (18.8)	13 (19.7)	25 (19.2)	
Present	52 (81.3)	53 (80.3)	105 (80.8)	
Fungal elements				0.02
Absent	51 (81.0)	55 (94.8)	106 (87.6)	
Present	12 (19.0)	3 (5.2)	15 (12.4)	
Charcot-Leyden crystals				0.97
Absent	52 (82.5)	48 (82.8)	100 (82.6)	
Present	11 (17.5)	10 (17.2)	21 (17.4)	
Eosinophil aggregates				0.58
Absent	42 (67.7)	42 (72.4)	84 (70.0)	
Present	20 (32.3)	16 (27.6)	36 (30.0)	

hpf = High power field.

period. Of these, 130 had a structured histopathology report and became eligible for the study. Their mean age was 54.7 years (women 52.4 years; men 56.9 years; $p = 0.10$). Similar numbers of men and women underwent ESS (49.2% women, 50.8% men). There was similar representation of CRSwNP and CRS without nasal polyps subtypes in both genders; CRSwNP occurred in 50.8% of the patients ($p = 0.60$).

Lund-Mackay and SNOT-22 Scores

SNOT-22 scores are presented in Table 2. A preoperative sinus CT score as calculated *via* the Lund-Mackay system was similar for both genders (women, 11.0; men, 11.5 [$p = 0.62$]). However, women versus men had significantly higher preoperative SNOT-22

scores (48.7 versus 38.0; $p = 0.004$). After surgery, women versus men showed more reduction in SNOT-22 scores from baseline at 3 months (mean reduction of -33.2 versus -25.0 ; $p = 0.02$). Women and men showed equal and significant improvement at 6 months (mean reduction of -28.1 and -23.8 , respectively; $p = 0.31$) and 12 months (mean reduction of -24.5 and -20.8 , respectively; $p = 0.53$). However, at 24 months, the women versus men showed a more significant reduction in SNOT-22 scores from baseline (mean reduction of -35.0 versus -15.9 ; $p = 0.02$).

Histopathology Reports

Histopathology reports are presented in Table 3. All 130 patients selected had completed histopathology reports. Differences in the

Table 4 Comparison of serum absolute eosinophil count and IgE levels between the men and women in the study

	Women (n = 64)	Men (n = 66)	Total (N = 130)	p Value
Absolute eosinophil count ($\times 10^9/L$)				
No.	61	63	124	
Closest to surgery, mean $\pm$ SD	0.4 $\pm$ 0.5	0.3 $\pm$ 0.3	0.3 $\pm$ 0.4	0.42
Highest, mean $\pm$ SD	0.5 $\pm$ 0.6	0.5 $\pm$ 0.6	0.5 $\pm$ 0.6	0.58
Serum IgE level (kU/L)				
No.	24	26	50	
Closest to surgery, mean $\pm$ SD	433.3 $\pm$ 510.0	190.8 $\pm$ 196.4	307.2 $\pm$ 395.9	0.04
Highest, mean $\pm$ SD	435.0 $\pm$ 509.4	190.8 $\pm$ 196.4	308.0 $\pm$ 395.8	0.04

IgE = immunoglobulin E; SD = standard deviation.

overall degree of inflammation present in the sinonasal tissue between the two genders was not statistically significant ($p = 0.16$). Other markers that looked at severity of inflammation were also similar between the two genders and are detailed in Table 3.

Serum Eosinophil and IgE Levels

Serum eosinophil and IgE levels are presented in Table 4. Of the 130 patients eligible for the study, a total of 124 patients had eosinophil count measurements recorded (61 women, 63 men). Women and men had a similar absolute eosinophil count when the value obtained closest to surgery date was studied (a mean eosinophil count of $0.4 \times 10^9/L$ and $0.3 \times 10^9/L$, respectively; $p = .41$) and also when the highest recorded value was studied (a mean eosinophil count of $0.5 \times 10^9/L$ for both genders; $p = 0.58$). Fifty patients had serum IgE measurements recorded (24 women, 26 men). Women showed significantly higher serum IgE values than did men. This was true whether the value obtained closest to surgery was studied (a mean IgE value of 433.3 kU/L in the women versus 190.8 kU/L in the men [$p = 0.04$]) or the highest recorded value of IgE was studied (435.0 kU/L in women versus 190.8 kU/L in men [$p = 0.04$]).

Up to this point, the analysis of the data was entirely agnostic of the details of the subjects and unbiased in the study of serologic histopathologic characteristics. On noting the presence of fungal elements and elevated IgE levels in women, further analysis on clinical characteristics was conducted. Allergic fungal sinusitis (AFS) was found significantly more commonly in the female versus the male patients (21.9% versus 9.1%; $p = 0.04$). AERD was present in 15.0% and had similar representation between the genders ($p = 0.2$). The prevalence of asthma was similar between the women and men (48%; $p = 0.80$). Similar prevalences of depression (12.4%; $p = 0.66$) and anxiety (10.2%; $p = 0.35$) were noted between the two genders. Women versus men had significantly higher rates of migraines (19.4% versus 4.6%; $p = 0.01$) and overall primary headaches disorders (23% versus 6.2%; $p = 0.007$).

DISCUSSION

The primary goal of this study was to identify gender differences in histopathology and serum IgE and eosinophils levels of patients with CRS. We are not aware of other studies that looked at gender differences in CRS histopathology. Our primary goals were to study tissue and serologic characteristics. A higher rate of fungal elements was identified in postoperative histopathology reports of the female patients. As noted, a secondary follow-up analysis was performed to review the prevalence of AFS, which was found to be significantly more common in the women ($p = 0.04$). The finding of tissue fungal elements may have impacted the clinical diagnosis. The prevalence of AERD was similar between the two genders. These findings are of interest when studied in context to the higher prevalence of AERD reported in women by the Mendolia-Loffredo *et al.*⁵

Both AERD and AFS are usually characterized by more severe and recalcitrant disease.^{1,2} Our surgical cohort is too small to make

any extrapolations to the general population, but when studied in context with the study by Mendolia-Loffredo *et al.*,⁵ we propose that, in cohorts in which women reported higher symptom scores, more severe or recalcitrant forms of CRS may be potential drivers of higher symptomatology. Further research is required to fully understand the effect that the endotype of CRS disease could have on symptomatology in general and on how it would relate to the observed gender differences in symptom severity. Previous studies that compared socioeconomic and demographic factors in AFS and CRS did not find gender alone to be a significant factor.^{14–16} However, Wise *et al.*¹⁴ also found that white women with bone erosion from AFS presented for management ~12 years later than African American patients. Lu-Myers *et al.*¹⁶ reported that patients with AFS have higher IgE levels, which was also found to be true in the women in our cohort.

Differences in total serum IgE levels in women with CRS compared with men with CRS were a novel finding. In the general U.S. population, total serum IgE levels are actually higher in men compared with women (55.9 kU/L in men versus 34.0 kU/L in women).¹⁷ Furthermore, in the CRS subtype in which the total IgE value is expected to be very high (e.g., AFS), there are once again no clear gender differences reported in previous studies.^{15,16} Even though AFS and the presence of tissue fungal elements are not necessarily synonymous entities, the AFS subtype could potentially explain the higher levels of serum IgE seen in the women. We found no significant correlation between total IgE values and sinus CT imaging findings. These were contrary to the findings reported by Baroody *et al.*¹² but consistent with a report by Poznanovic and Kingdom.¹⁸ The significance of total serum IgE levels in CRS is as yet not completely understood because the total IgE value does not change after surgery and clinical improvement.¹⁹ Results of studies that show benefit of monoclonal antibodies directed against IgE also seem to confer benefit independent of the IgE level.²⁰ Another possible explanation of our findings could be that higher total serum IgE levels are related to staphylococcal enterotoxins; a previous study found an association between culture results and total serum IgE values.²¹

Earlier deployment of ESS may be beneficial in superior control of sinonasal symptoms and asthma.²² Because women are reported to have higher disease symptomatology as well as a higher prevalence of CRS, it behooves us to investigate why the rate of ESS in men and women with CRS continue to be similar.³ The presence of comorbid migraines, primary headache disorders, and depression may have an impact on surgeons for offering ESS to female patients with CRS. However, surgeons should also become aware that objective metrics such as higher serum IgE levels and a higher prevalence of more severe CRS phenotypes such as AFS and AERD may also have a role in worsened symptom burden in women. As with any implicit bias, the rhinologic surgeon should become more aware of gender-based preferences in offering ESS for CRS because

physician preference can have a greater effect on decision-making for elective surgeries.

Limitations of Our Study

Our study was limited by a relatively small sample size and the retrospective nature of data collection. The standardized histopathology report was initially performed only by select pathologists before being adopted routinely by the group in the year 2013, and, hence, this report was not available for the entire group of patients who underwent ESS in the study period. IgE and eosinophil levels were not available for all the patients. Serum eosinophil data were available in 124 patients (61 women, 63 men) and IgE levels in 50 patients (24 women, 26 men). This was a limitation due to the retrospective nature of our study. However, the data on IgE levels were present in similar numbers of males and females patients, and the differences were statistically significant. A prospective study would best address this limitation and is a future focus.

We also did not collect data on the time interval between the IgE level measurement and surgery. IgE testing was ordered before surgery as a workup for CRS subtyping. A previous study by Lal *et al.*¹⁹ showed that IgE levels do not significantly change even 12 months after surgery. Because the same method of data collection applied to both genders, we hoped that the results of our study were not significantly influenced by the time interval to surgery. Also, multiple confounding variables could exist that could influence the difference in IgE observed between the genders. We did collect comprehensive data on asthma and found no difference in the prevalence of asthma between the two genders. However, other chronic diseases could potentially influence IgE levels,²³ and some of those were outside the scope of our study.

This study also used an overlapping cohort from our previous studies on gender differences in CRS and reports on some common patients.^{3,4} However, we expanded the study period to 2013–2014 and excluded patients from 2011–2013 who did not have standardized reports, which resulted in a smaller, distinct group. The study may have been underpowered to detect other elements on differences in the histopathology report. In addition, accurate information on the use of perioperative topical and systemic corticosteroids that may have also impacted the tissue histopathology was not available. We also recognized that the higher percentage of women who met clinical criteria for AFS may be reflected in the histopathology and serum IgE levels, and may not be independent findings. The finding of a higher SNOT-22 burden in female patients with CRS was consistent in this current cohort as well, but we remain very aware that, to extrapolate our findings to the general population, prospective, multicentered studies are necessary. The greater burden of migraine and primary headache disorder (diagnosed based on the International Head Society Diagnostic criteria^{24,25}) in women could also contribute to their higher symptom scores.

Sedaghat *et al.*²⁶ published about the associations between objective clinical and demographic characteristics of patients with CRS. A logical progression is to study the association of SNOT-22 and histopathologic characteristics in subjects with CRS. Given the number of elements in the SNOT-22 questionnaire, as well as in the structured histopathology report, a meaningful study requires a larger cohort of patients. As data in more patients become available in the future, the association of specific histopathologic characteristics with total SNOT-22 scores and SNOT-22 subdomains will be studied. Studies of gender-based differences are essential to deliver superior patient care. Although such data in the field of CRS are scarce, increasingly, commentary is being directed to gender-based characteristics of patients with CRS.²⁷ Multi-institutional collaborative studies with larger cohorts will offer critical insights to gender-based differences in CRS.

CONCLUSION

Women who underwent ESS for CRS had a higher SNOT-22 symptom burden. Worsened symptomatology may be secondary to a higher prevalence of primary headache disorders in women. However, surgeons should also be aware that female patients with CRS who seek ESS may have a higher prevalence of severe disease endotypes (more tissue fungal elements, elevated serum IgE levels) and phenotypes (AFS, AERD).

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