Association between Asthma and Chronic Rhinosinusitis Severity in the Context of Asthma Control

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Abstract

Objective. Comorbid asthma is associated with decreased quality of life (QOL) in chronic rhinosinusitis (CRS). It is unclear whether this association is independent of the patients’ clinical asthma status. We therefore sought to determine if asthma is associated with lower QOL in CRS, independent of asthma control.

Study Design. Cross-sectional cohort study of 350 patients with CRS.

Setting. Tertiary academic rhinology clinic.

Subjects and Methods. In total, 350 participants with CRS were recruited and 28.3% were asthmatic. CRS-specific QOL was measured using the 22-item Sinonasal Outcome Test (SNOT-22). Asthma control was assessed with the Asthma Control Test (ACT). General health-related QOL was assessed with the EuroQOL 5-dimensional general health-related quality of life survey visual analog scale (EQ-5D VAS). Associations were sought between SNOT-22 and EQ-5D VAS (dependent variables) and asthma (independent variable), while controlling for ACT. ACT score for patients with CRS without asthma was set at 25 (indicating completely controlled, asymptomatic asthma).

Results. Comorbid asthma was associated with SNOT-22 ($\beta = 11.8; 95\% \text{ confidence interval (CI)}: 6.2$-$17.3; \text{P} < .001) and EQ-5D VAS ($\beta = -6.2; 95\% \text{ CI}, -11.2$ to $-1.3; \text{P} = .014$). After controlling for ACT, asthma was no longer associated with SNOT-22 ($\beta = .147$ and EQ-5D VAS ($\beta = .994$). Instead, ACT score was associated with SNOT-22 ($\beta = -2.1; 95\% \text{ CI}, -3.2$ to $-1.1; \text{P} < .001$) and EQ-5D VAS ($\beta = 2.1; 95\% \text{ CI}, 1.1$ to $3.0; \text{P} < .001$). ACT score completely drove the association between asthma and worse QOL.

Conclusion. Comorbid asthma is not necessarily reflective of decreased QOL in CRS. The association of comorbid asthma with lower QOL in CRS is related to the clinical status (eg, control) of asthma.

Keywords

chronic rhinosinusitis, CRS, sinonasal symptoms, asthma, asthma control test, ACT, SNOT-22, EQ5D-VAS

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Chronic rhinosinusitis (CRS) is an inflammatory disease of the sinonasal mucosa that causes a significant decrease in patients’ quality of life (QOL). This decrease in QOL is typically due to chronic sinonasal symptomatology, acute CRS exacerbations, and comorbid pulmonary conditions. Previous studies have highlighted the heterogeneous nature of this disease by identifying multiple inflammatory mechanisms as potential etiologic agents of CRS, which may all lead to the chronic airway inflammation and clinical phenotype that define the disease.

As inflammatory disorders of airway mucosa, asthma and CRS are commonly comorbid. Over 40% of patients diagnosed with asthma have comorbid CRS, and 50% of patients with CRS with nasal polyps also have asthma. The epidemiologic relationship between CRS and asthma forms the basis of the “unified airway theory,” which is supported by evidence that antigenic stimulation of one site can trigger an inflammatory reaction in the other and that their

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development may be related.13-18 In addition, prior studies have shown that medical treatment of rhinitis or rhinosinusitis can lead to improved pulmonary outcomes in asthmatic patients.19-21

Previous studies have linked the diagnosis of asthma to greater severity of CRS disease. In particular, asthmatic patients have been shown to have worse radiographic CRS disease severity based on Lund-MacKay scores,22 and those with worse asthma severity have higher Lund-MacKay scores.23 CRS has also been associated with increased frequency of asthma exacerbations,4,24 and increasing sinonasal symptom severity has been associated with decreased asthma control in patients with CRS and asthma.2,26 Despite this prior work, the nature of the exact associative relationship between comorbid asthma and the severity of sinonasal symptomatology in CRS remains unclear.

In this study, we sought to characterize the association between asthma and patient-reported outcome measures (PROMs) of CRS, including sinonasal symptomatology and general health-related QOL. Since the specific impact of asthma on asthmatics may be highly variable depending on the clinical status of the asthma,27 we also sought to determine how any association between asthma and CRS-related PROMs might be affected by the degree of asthma control. Asthma control is a well-established and measurable outcome measure for asthma that encompasses the frequency of symptom exacerbations, the need for rescue medications, and the overall impact of the disease on a patient’s day-to-day activities.27 We hypothesized that asthma would be associated with more severe sinonasal symptoms and decreased general health-related QOL and that this association would be modified by the degree of asthma control experienced by asthmatic patients with CRS.

**Methods**

**Study Participants**

The Massachusetts Eye and Ear Infirmary Human Studies Committee approved this study. We prospectively recruited adult patients aged 18 years or older who met established consensus guideline criteria for CRS.28 All study participants provided informed consent for inclusion in this study. To narrow the study population to patients with CRS and avoid any patients with systemic disease with sinonasal manifestations, exclusion criteria were created, including comorbid diagnoses of vasculitis, cystic fibrosis, sarcoidosis, and immunodeficiency. Also, to avoid confounding results due to treatment, any patient who had undergone sinonasal surgery in the past 6 months was excluded.

**Study Design and Data Collection**

This is a cross-sectional cohort study. A total of 350 study participants were recruited. All data were collected at the time of enrollment into the study. The age, sex, race, history of sinus surgery, intranasal steroid use, and smoking history of all participants were recorded from each participant. At enrollment, participants were asked by the evaluating rhinologist to report a history of aeroallergen hypersensitivity based on formal allergy testing and aspirin sensitivity based on a clinical history or formal testing. The presence of nasal polyps was determined based on nasal endoscopy by the evaluating rhinologist. Patients were considered asthmatic from prior diagnosis made based on clinical consensus guidelines.29 All asthmatic patients were being treated with at least an albuterol rescue inhaler, to be used on an as-needed basis. Asthmatic patients were also asked to report whether they were using an inhaled corticosteroid at the time of enrollment. All participants completed a 22-item Sinonasal Outcome Test (SNOT-22)30 survey to measure CRS symptom severity and the EuroQol 5-dimensional (EQ-5D) general health survey and visual analog scale (EQ-5D VAS),31 which reflects general health-related QOL. Asthma control was assessed with the Asthma Control Test (ACT).32,33

**Statistical Analysis**

All analysis was performed with the statistical software package R (www.r-project.org). Patients with CRS without asthma were assigned an ACT score of 25, which is the maximum score possible and indicates completely controlled, asymptomatic asthma. All associations with asthma (as an independent variable) and SNOT-22 and EQ-5D VAS scores (as dependent variables) were investigated with linear regression analysis. Multivariable models were then used to evaluate these associations controlling for participant age, sex, aeroallergen hypersensitivity, polyps, and intranasal steroid use. Next, we controlled for asthma control by including ACT scores in the multivariable model. Multivariable models used to study these associations controlled for participant age, sex, aeroallergen hypersensitivity, asthma, polyps, and intranasal steroid use.

**Results**

**Characteristics of Study Participants**

A total of 350 patients (51.3% male, 48.7% female) were enrolled in the study with a mean (standard deviation [SD]) age of 51.9 (15.7) years (95% confidence interval [CI], 21.9-79.8), and their characteristics are summarized in Table 1. Of those enrolled, 28.3% had a history of asthma, 24.9% were active or former smokers, and 45.7% had a history of aeroallergen hypersensitivity. With respect to CRS characteristics, 43.1% of study participants had nasal polyps and 34.0% had undergone prior endoscopic sinus surgery. The mean (SD) SNOT-22 score was 32.7 (22.0; 95% CI, 1-80), and the mean (SD) EQ-5D VAS score was 74.4 (18.6; 95% CI, 24-100). Among patients with asthma, the mean (SD) ACT score was 20.1 (4.8; 95% CI, 8-25), and 48.5% were on a long-term inhaled corticosteroid.

**Asthma Status Is Associated with Sinonasal QOL**

In this study, we first determined that asthma was associated with worse sinonasal QOL, as reflected by higher SNOT-22, on univariate analysis ($\beta = 13.7; 95\% \text{ CI}, 8.8-18.6; P < .001$). We then tested whether asthma was associated with
the SNOT-22 score in multivariable linear regression analysis controlling for age, sex, smoking, polyps, aeroallergen hypersensitivity, and intranasal steroid use. Using this multivariable model, asthma was still associated with lower EQ-5D VAS scores (β = −5.3; 95% CI, −9.6 to −1.0; P = .016). After controlling for age, sex, smoking, polyps, aeroallergen hypersensitivity, and intranasal steroid use, asthma remained associated with lower EQ-5D VAS scores (β = −6.2; 95% CI, −11.2 to −1.3; P = .014). However, there was no longer a statistically significant association between asthma and EQ-5D VAS (β = 0.0; 95% CI, −7.2 to 7.3; P = .994) after adding ACT score as a covariate to our multivariable model. In contrast, while simply having comorbid asthma was not associated with EQ-5D VAS, in this multivariable model, ACT score was significantly associated with EQ-5D VAS scores (β = 2.1; 95% CI, 1.1-3.0; P < .001). As was the case with sinonasal QOL, stratifying study participants by the presence of nasal polyps or smoking status did not qualitatively change the associations between comorbid asthma, ACT score, and EQ-5D VAS. For participants with or without nasal polyps, who were smokers or nonsmokers, ACT score was significantly associated with EQ-5D VAS while just having comorbid asthma was not using our multivariable model.

### Discussion

Asthma and comorbid CRS are heavily linked epidemiologically, and up to 40% of asthmatics have comorbid CRS. Previous studies have evaluated the impact of CRS on comorbid asthma and have shown that in asthmatic patients, comorbid CRS is associated with increased frequency of emergency room visits, hospitalizations, and systemic corticosteroid use secondary to asthma. Asthmatics with comorbid CRS have also been shown to have worse pulmonary function and decreased asthma-specific and general QOL outcomes than patients with asthma alone. In comparison, comorbid asthma in CRS has been shown to be associated with worse radiographic evidence of sinus disease than nonasthmatic patients with CRS, and greater asthma severity is associated with worse radiographic disease in patients with CRS with asthma. Unfortunately, radiographic evaluation of CRS has not been shown to correlate well with PROMs. While it is intuitive that patients with asthma and CRS have an overall worse QOL and more severe sinonasal symptomatology, it remains unclear how this association is modulated by the clinical status of the asthma. Filling this gap in knowledge is important to both the clinician and patient as it provides information regarding the relationship between CRS and asthma. In this study, we found that while comorbid asthma was associated with more severe sinonasal symptomatology and worse general health-related QOL in CRS, this association was entirely dependent on the level of asthma control.

Previous work has demonstrated a clear clinical link in the disease courses of CRS and asthma when these conditions are concomitantly present. The severity of CRS is associated with the degree of asthma control in asthmatic patients with CRS. In addition, treatment of CRS has been shown to improve asthma outcome measures in asthmatic patients with CRS. Medical and surgical treatment of CRS in children with asthma has been shown to decrease...
Comorbid asthma is associated with worse CRS-specific and general health-related QOL. However, this association is entirely driven by the level of asthma control such that comorbid asthma is not associated with worse QOL in patients with CRS when asthma control is taken into account. These findings indicate that the diagnosis of asthma is not necessarily predictive of worse CRS symptom severity in patients with good asthma control.

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Author Contributions

Adam P. Campbell, acquisition, analysis, and interpretation of data; drafting and revising the manuscript; Katie M. Phillips, acquisition, analysis, and interpretation of data; revising the manuscript; Lloyd P. Hoehle, acquisition, analysis, and interpretation of data; revising the manuscript; Robert A. Gaudin, acquisition, analysis, and interpretation of data; revising the manuscript; David S. Caradonna, acquisition, analysis, and interpretation of data; revising the manuscript; Stacey T. Gray, acquisition, analysis, and interpretation of data; drafting and revising the manuscript.

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References

R. A single nasal allergen challenge increases induced sputum
inflammatory markers in non-atopic subjects with seasonal
allergic rhinitis: correlation with plasma interleukin-5. Clin
Exp Allergy. 2003;33:475-482.

11. Braunstahl GJ, Overbeek SE, Kleinjan A, Prins JB,
Hoogsteden HC, Fokkens WJ. Nasal allergen provocation
induces adhesion molecule expression and tissue eosinophilia
107:469-476.

12. Braunstahl GJ, Overbeek SE, Kleinjan A, Prins JB,
Hoogsteden HC, Fokkens WJ. Segmental bronchial provoca-
tion induces nasal inflammation in allergic rhinitis patients.

association with chronic rhinosinusitis: the GA2LEN survey in

14. Dixon AE. Rhinosinusitis and asthma: the missing link. Curr

15. Seybt MW, McMains KC, Kountakis SE. The prevalence and
effect of asthma on adults with chronic rhinosinusitis. Ear

16. Slavin RG. The upper and lower airways: the epidemiological
and pathophysiological connection. Allergy Asthma Proc.
2008;29:553-556.

17. Maesano A. Epidemiological evidence of the occurrence of

18. Chen YT, Chien CY, Tai SY, Huang M, Lee CT. Asthma
associated with chronic rhinosinusitis: a population-based

19. Rachelefsky GS, Katz RM, Siegel SC. Chronic sinus disease

20. Watson WT, Becker AB, Simons FE. Treatment of allergic
rhinitis with intranasal corticosteroids in patients with mild
asthma: effect on lower airway responsiveness. J Allergy Clin

21. Tsao CH, Chen LC, Yeh KW, Huang JL. Concomitant chronic
sinusitis treatment in children with mild asthma: the effect on

between severity of chronic rhinosinusitis and nasal polyposis,

severity of asthma and degree of chronic rhinosinusitis. Am J

24. ten Brinke A, Sterk PJ, Mascllee AA, et al. Risk factors of fre-
quent exacerbations in difficult-to-treat asthma. Eur Respir J.

difficult asthma are independent risk factors for frequent

rhinosinusitis and asthma: a questionnaire-based study.

new GINA strategy: a roadmap to asthma control. Eur Respir

28. Rosenfeld RM, Andes D, Bhattacharyya N, et al. Clinical prac-

29. Expert Panel Report 3: guidelines for the diagnosis and man-
agement of asthma. 2007. www.nhlbi.nih.gov/guidelines/


208.

the asthma control test: a survey for assessing asthma control.

33. Schatz M, Sorkness CA, Li JT, et al. Asthma control test:
reliability, validity, and responsiveness in patients not previ-
ously followed by asthma specialists. J Allergy Clin Immunol.
2006;117:549-556.

34. Ivanova JI, Bergman R, Birnbaum HG, Colice GL, Silverman
RA, McLaurin K. Effect of asthma exacerbations on health
care costs among asthmatic patients with moderate and severe
persistent asthma. J Allergy Clin Immunol. 2012;129:1229-
1235.

35. Ek A, Middelveld RJ, Bertilsson H, et al. Chronic rhinosinus-
itis in asthma is a negative predictor of quality of life: results
from the swedish GA2LEN survey. Allergy. 2013;68:1314-
1321.

36. Wabnitz DA, Nair S, Wormald PJ. Correlation between preo-
perative symptom scores, quality-of-life questionnaires, and
staging with computed tomography in patients with chronic

review and meta-analysis of asthma outcomes following endo-
sopic sinus surgery for chronic rhinosinusitis. Int Forum

Management of chronic rhinosinusitis with nasal polyps and
coeXisting asthma: a systematic review. Am J Rhinol Allergy.

39. Batra PS, Tong L, Citardi MJ. Analysis of comorbidities and
objective parameters in refractory chronic rhinosinusitis.