

Changes in chronic rhinosinusitis symptoms differentially associate with improvement in general health-related quality of life

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ARTICLE INFO

Article history:

Received for publication March 22, 2018.

Received in revised form May 12, 2018.

Accepted for publication May 23, 2018.

ABSTRACT

Background: Previous work has shown that the symptoms of chronic rhinosinusitis (CRS) differentially associate with decreased general health-related quality of life (QOL).

Objective: We sought to determine whether longitudinal changes in different types of CRS symptomatology lead to correspondingly different magnitude changes in general health-related QOL.

Methods: Prospective observational study of 145 patients undergoing medical management for CRS. Chronic rhinosinusitis symptom severity was measured using the 22-item Sinonasal Outcome Test (SNOT-22) and associated nasal, sleep, ear/facial discomfort, and emotional subdomains of the SNOT-22. General health-related QOL was measured using the 5-dimensional EuroQoL questionnaire's visual analog scale (EQ-5D VAS). These data were collected at 2 time points: at enrollment and at a subsequent follow-up visit within the next 2 to 6 months. Associations were sought between the changes in SNOT-22 and EQ-5D VAS.

Results: The change in SNOT-22 was associated with change in EQ-5D VAS (adjusted linear regression coefficient [β] = -0.37 , 95%CI: -0.51 to -0.24 , $P < .001$). The change in EQ-5D VAS was only associated with changes in the sleep (adjusted β = -0.42 , 95% confidence interval [95%CI]: -0.81 to -0.04 , $P = .034$) and ear/facial discomfort (adjusted β = -1.00 , 95%CI: -1.89 to -0.10 , $P = .031$) subdomains but not nasal (adjusted β = -0.12 , 95%CI: -0.52 to 0.28 , $P = .564$) or emotional (adjusted β = -0.17 , 95%CI: -1.83 to 1.49 , $P = .840$) subdomains.

Conclusion: Changes in the severity of sleep and ear/facial discomfort symptoms associate most greatly with the change in general health-related QOL that CRS patients experience during routine medical management. Reduction of these extranasal symptoms of CRS may therefore lead to the greatest improvement in general health-related QOL.

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Introduction

Chronic rhinosinusitis (CRS) is an inflammatory disease of the paranasal sinus mucosa.¹ Chronic rhinosinusitis is characterized by nasal as well as extranasal symptoms related to poor sleep, ear/facial discomfort, and emotional disturbance.² Because of these associated symptoms as well as other clinical manifestations—such as acute exacerbations of CRS and exacerbation of comorbid pulmonary disease—CRS causes a significant quality of life (QOL) detriment.^{3–5} The clinical manifestations of CRS are also associated

with significant productivity losses.⁶ Between direct costs associated with treatment and physician visits and indirect costs related to lost productivity, CRS is associated with billions of dollars of cost to society every year.⁷

Previous work has suggested that the clinical manifestations of CRS may differentially associate with (and possibly drive) the downstream consequences of CRS.^{3,8} Clinically, the most prominent manifestations of CRS are its associated symptomatology, and the most significant consequence of CRS is the decreased QOL that is experienced by patients.¹ We have previously reported that the burden of symptoms related to poor sleep and ear or facial discomfort were most associated with decreased QOL in CRS.³ Interestingly, we have also found this to be the case in allergic rhinitis.⁹ These findings point to the particularly bothersome nature of extranasal symptoms of inflammatory sinonasal disease in reducing patients' QOL.

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Disclosures: None.

<https://doi.org/10.1016/j.anai.2018.05.029>

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These findings also raise the possibility that improvement of sleep or ear or facial discomfort may have the greatest impact on improving QOL in patients with CRS. However, prior work on this matter has been cross-sectional in nature and therefore only suggestive of this possible therapeutic strategy. As such, the importance of nasal vs extranasal symptoms of CRS in affecting patients' QOL remains unclear. Moreover, the possibility of differentially improving QOL by therapeutically targeting these symptoms remains unclear as well. To gain greater insights into these issues, we therefore performed a longitudinal study of patients who were treated medically for CRS. Based on our prior work, we hypothesized that changes in the severity of extranasal symptoms related to sleep quality and ear or facial discomfort would be associated with the greatest reciprocal changes in these patients' QOL. We believe that our results will be important in establishing specific types of CRS symptomatology as targets for specific therapeutic interventions.

Methods

Study Participants

This study was granted ethical clearance by the Massachusetts Eye and Ear Infirmary Human Studies Committee. Adult patients (age 18 years or older) with CRS were recruited prospectively from the Massachusetts Eye and Ear Infirmary Sinus Center and provided written informed consent for inclusion into this longitudinal study. All participants met consensus guideline established criteria for CRS.¹⁰ To remove the confounding effects of systemic inflammatory conditions that could be causing the patients' CRS, exclusion criteria included comorbid diagnoses of: 1) vasculitis, 2) cystic fibrosis, 3) sarcoidosis, and 4) immunodeficiency. Patients with active, acute CRS exacerbations at either study time point were excluded to remove any confounding effects of acute CRS exacerbations. To remove the confounding effect of recent endoscopic sinus surgery, patients who had endoscopic sinus surgery within 6 months preceding enrollment or during the study period were also excluded.

Study Design and Data Collection

This study was designed as a prospective observational study. Data were collected at the time of enrollment and at a second time point, which was a routine clinical follow-up visit, 2 to 6 months after enrollment. During the treatment period, patients were treated medically for CRS, using intranasal saline irrigation and intranasal corticosteroids. Systemic adjunctive medications, such as oral antibiotics or oral corticosteroids, were used on a patient-by-patient basis. At the time of enrollment, demographic and clinical characteristics of patients were collected. Demographic information collected included age, sex, and race. Any patient who was an active smoker or reported a history of being a tobacco smoker in the past was considered to be a smoker for this study.¹¹ At enrollment, participants were assessed by the evaluating physician for a history of asthma based on clinical history and prior diagnosis. A history of aeroallergen hypersensitivity was based on formal skin or serological allergy testing to aeroallergens, including house dust mite, molds, grasses, trees, weeds, and cockroach. Participants were interviewed to determine whether they had a history of previous sinus surgery and a history of aspirin sensitivity. For each participant, the presence of nasal polyps was determined by nasal endoscopy.

Patient-Reported Outcome Measures

General health-related QOL was measured using the visual analog scale (VAS) from the validated EuroQol 5-dimensional (EQ-5D) questionnaire.¹² The EQ-5D VAS assesses patients' self-reported current state of health—with 0 as the minimum, representing the

"worst health you can imagine," and 100 as the maximum, representing the "best health you can imagine." All participants also completed the validated 22-item Sinonasal Outcome Test (SNOT-22) survey,¹³ which provides a quantitative measure of CRS symptom burden ranging from 0 to 110, with higher scores reflecting greater CRS symptom burden. Prior work has validated the presence of 4 subdomains of the SNOT-22 (reflecting nasal, ear/facial discomfort, sleep, and emotional symptoms).¹⁴ As previously described and validated,¹⁴ the SNOT-22 nasal subdomain score was calculated by summing SNOT-22 items 1 through 6, 21, and 22, with a range of 0 to 40. The SNOT-22 ear/facial discomfort subdomain score was calculated by summing SNOT-22 items 7 through 10 with a range of 0 to 20. The SNOT-22 sleep subdomain score was calculated by summing SNOT-22 items 11 through 18, with a range of 0 to 40. The SNOT-22 emotional subdomain score was calculated by summing SNOT-22 items 19 and 20, with a range of 0 to 10. The SNOT-22 and EQ-5D were completed by each participant at enrollment and at the second time point.

Statistical Analysis

All analysis was performed using the statistical software package R version 3.2.5 (www.r-project.org).¹⁵ Correlations were calculated using Spearman correlation. Associations were sought using linear regression. A total of 145 participants were recruited to have at least 80% power to detect an association of medium effect size (Cohen's $f^2 = 0.15$) between change in EQ-5D VAS (as dependent variable) and 11 total variables (changes in each of the 4 SNOT-22 subdomain scores as the independent variables of interest and 7 covariates: age, sex, smoking history, comorbid asthma, aeroallergen hypersensitivity, nasal polyps, and previous sinus surgery) at a significance level of .05.

Results

Characteristics of Study Participants

A total of 145 participants were recruited, and their characteristics are described in Table 1. These participants were treated medically for CRS for a mean time of 104 days (standard deviation [SD], 33 days). Over that period, the mean change in SNOT-22 score was -11.4 (SD, 20.5), and the mean change in EQ-5D VAS was 1.4 (SD, 18.4).

Cross-Sectional Association between CRS Symptoms and General Health-Related QOL

As expected, both at the time of enrollment and at the follow-up time point, CRS symptom burden, as reflected by the SNOT-22 score and its associated subdomain scores, was negatively correlated with general health-related QOL. Moreover, sleep and ear or facial discomfort symptoms had the greatest magnitude of negative correlation with general health-related QOL. At the time of enrollment, the total SNOT-22 score was negatively correlated with EQ-5D VAS ($\rho = -0.51$, 95%CI: -0.61 to -0.38 , $P < .001$). The nasal ($\rho = -0.37$, 95%CI: -0.51 to -0.22 , $P < .001$), sleep ($\rho = -0.50$, 95%CI: -0.62 to -0.37 , $P < .001$), ear/facial discomfort ($\rho = -0.38$, 95%CI: -0.51 to -0.23 , $P < .001$), and emotional ($\rho = -0.35$, 95%CI: -0.49 to -0.20 , $P < .001$) SNOT-22 subdomain scores were all negatively correlated with EQ-5D VAS. We found similar results cross-sectionally at the follow-up time point when the total SNOT-22 score was negatively correlated with EQ-5D VAS ($\rho = -0.46$, 95%CI: -0.58 to -0.33 , $P < .001$). Similarly, the nasal ($\rho = -0.38$, 95%CI: -0.52 to -0.23 , $P < .001$), sleep ($\rho = -0.44$, 95%CI: -0.56 to -0.30 , $P < .001$), ear/facial discomfort ($\rho = -0.39$, 95%CI: -0.52 to -0.25 , $P < .001$), and emotional ($\rho = -0.30$, 95%CI: -0.44 to -0.15 , $P < .001$) SNOT-22

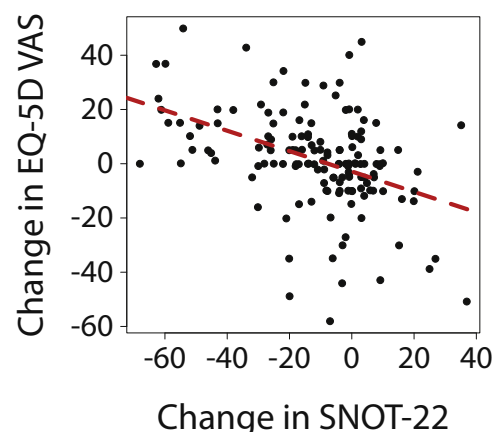
Table 1
Characteristics of Study Participants

	Study participants (N = 145)
Demographics	
Age, mean in years (SD)	51.2 (16.5)
Sex	
Male	51.0%
Female	49.0%
Past/present smoker	34.5%
Comorbidities	
Aeroallergen hypersensitivity	49.7%
Aspirin sensitivity	4.8%
Asthma	37.2%
CRS characteristics	
Nasal polyps	52.4%
Previous sinus surgery	42.8%
At enrollment	
SNOT-22 score, mean (SD)	40.6 (23.8)
SNOT-22 subdomain scores, mean (SD)	
Nasal subdomain	17.1 (9.7)
Sleep subdomain	16.3 (11.3)
Ear/facial discomfort	5.6 (5.1)
Emotional	1.6 (2.3)
EQ-5D VAS, mean (SD)	71.1 (18.7)
At follow-up	
SNOT-22 score, mean (SD)	29.2 (21.1)
SNOT-22 subdomain scores, mean (SD)	
Nasal subdomain	13.3 (9.1)
Sleep subdomain	11.0 (10.3)
Ear/facial discomfort	4.0 (4.2)
Emotional	1.0 (1.8)
EQ-5D VAS, mean (SD)	72.5 (20.1)
Follow-up time, mean in days (SD)	104 (33)

subdomain scores were all negatively correlated with EQ-5D VAS at the follow-up time point as well.

Differential Association between Decreases in CRS Symptom Severities and Reciprocal Improvement in General Health-Related QOL

We sought to determine how changes in CRS symptom burden, as reflected by the SNOT-22 and its associated subdomain scores, would be associated with changes in general health-related QOL (Table 2). As expected, we found that the change in EQ-5D VAS was

**Figure 1.** Scatter plot of changes in EQ-5D VAS score vs changes in SNOT-22 score. Dotted line of best fit is superimposed.

negatively associated with change in the total SNOT-22 score on univariate ($\beta = -0.38$, 95%CI: -0.51 to -0.24 , $P < .001$) and multivariable ($\beta = -0.37$, 95%CI: -0.51 to -0.23 , $P < .001$) analyses. In other words, improvement (increase) in general health-related QOL (EQ-5D VAS) was associated with improvement (decrease) in total CRS symptom burden (SNOT-22 score) (Fig 1).

We next checked for association between changes in EQ-5D VAS and changes in individual SNOT-22 subdomain scores (Fig 2). We found that the change in EQ-5D VAS was significantly and negatively associated with changes in all individual subdomain scores (Table 2; $P \leq .02$ in all cases). However, using our multivariable model, which included all SNOT-22 subdomain scores as well as covariates including age, sex, smoking history, comorbid asthma, aeroallergen hypersensitivity, nasal polyps, and previous sinus surgery, we found that improvement in EQ-5D VAS was only significantly associated with improvement in sleep ($\beta = -0.42$, 95%CI: -0.81 to -0.04 , $P = .033$) and ear/facial discomfort ($\beta = -0.99$, 95%CI: -1.88 to -0.10 , $P = .032$) subdomain scores.

Discussion

Chronic rhinosinusitis is a heterogeneous disease with likely many different, patient-specific pathophysiologic mechanisms of development and persistence.¹⁶⁻²¹ Despite the great patient-to-patient heterogeneity in underlying pathophysiology, CRS uniformly converges on a common clinical presentation with downstream consequences exemplified by a significant detriment in QOL.^{1,22} Although other disease manifestations may contribute to decreased QOL, the chronic symptomatology associated with CRS is the most dominant disease manifestation that drives decreased QOL in affected patients.^{1,4,5,23,24} In further exploring the association of CRS symptomatology with decreased QOL, we have previously found that symptoms related to poor sleep and ear or facial discomfort were most greatly associated with decreased QOL.³ Highlighting the important association between these extranasal symptoms of inflammatory sinonasal disease and QOL, we have also found the same relationships to hold in allergic rhinitis as well.⁹ These findings raised the interesting possibility that direct intervention to reduce the severity of these extranasal symptoms in CRS could have the greatest impact to improve QOL. However, this hypothesis was inferred and based on a cross-sectional analysis. We therefore sought to further understand the relationship between different types of CRS symptoms and decreased QOL through longitudinal study. Specifically, we studied a cohort of patients undergoing evidence-based medical management of CRS and examined how their general health-related QOL improved in response to improvement in the

Table 2
Association Between Change in SNOT-22 Subdomain Scores and Change in EQ-5D VAS

	Univariate		Multivariable ^a	
	β (95% CI)	P value	β (95% CI)	P value
SNOT-22	-0.38 (-0.51 to -0.24)	<.001	-0.37 (-0.51 to -0.23)	<.001
SNOT-22 subdomains				
	Univariate β (95% CI)	P value	Multivariable ^b β (95% CI)	P value
Nasal	-0.61 (-0.91 to -0.30)	<.001	-0.12 (-0.52 to 0.27)	.546
Sleep	-0.75 (-1.04 to -0.45)	<.001	-0.42 (-0.81 to -0.04)	.033
Ear/facial discomfort	-1.56 (-2.22 to -0.89)	<.001	-0.99 (-1.88 to -0.10)	.032
Emotional	-1.82 (-3.33 to -0.31)	.020	-0.13 (-1.77 to 1.52)	.878

^aMultivariable model controls for age, sex, past/present smoking history, comorbid asthma, aeroallergen hypersensitivity, nasal polyps, and previous sinus surgery.

^bMultivariable model includes all SNOT-22 subdomains and also controls for age, sex, past/present smoking history, comorbid asthma, aeroallergen hypersensitivity, nasal polyps, and previous sinus surgery.

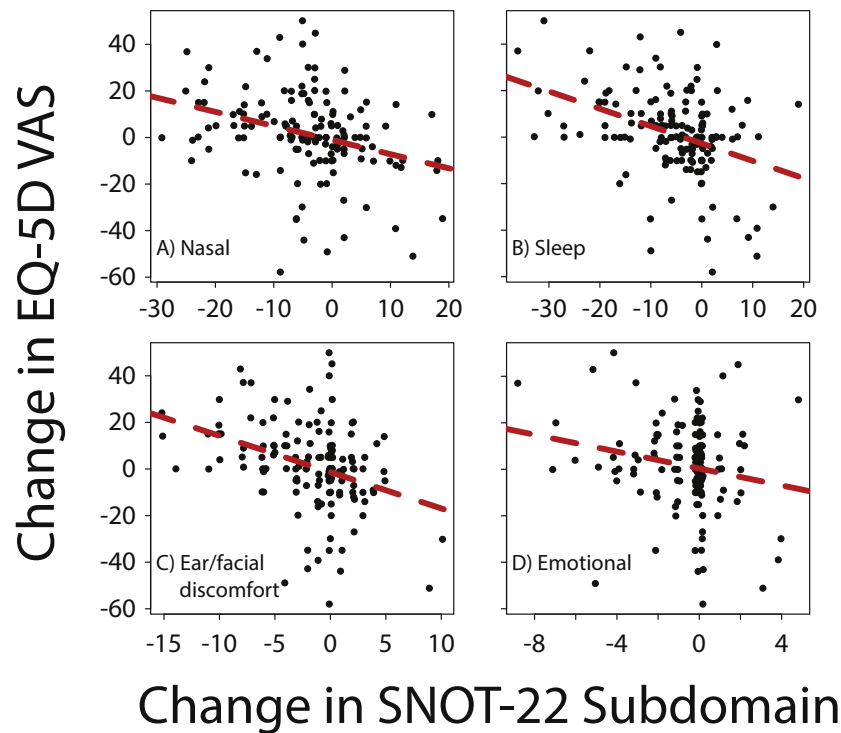


Figure 2. Scatter plots of changes in EQ-5D VAS vs changes in SNOT-22. A, nasal; B, sleep; C, ear/facial discomfort; and D, emotional subdomain scores. Dotted lines of best fit are superimposed.

different types of symptoms associated with CRS (nasal, poor sleep, ear or facial discomfort, emotional).^{2,14} We found that—consistent with our previous cross-sectional study—improvements in symptoms of sleep and ear or facial discomfort were associated with the greatest improvement in general health-related QOL.

Chronic rhinosinusitis has been well established to cause a QOL detriment that is similar to that caused by diseases such as heart disease, asthma, and diabetes.^{22,25} Treatment of CRS is therefore targeted to improving QOL, with particular emphasis on doing so through reduction of symptomatology.^{26–28} More recently, even as the medical treatment paradigm for CRS shifts away from nonspecific anti-inflammatory medications, such as corticosteroids, to pathophysiology-based treatments with biologicals,²⁹ the emphasis remains on improvement of QOL through reduction of symptomatology.^{30,31} However, as treatment for CRS becomes more specific and targeted for maximal efficacy, understanding which symptoms of CRS most dominantly drive decreased QOL is important—not only to better understand how medical therapies of CRS may be improving patients' QOL, but also because there may exist other therapies that can directly target those symptoms.

In this study, we showed that improvements in symptoms related to poor sleep and ear or facial discomfort are most associated with improvements in general health-related QOL in patients medically treated for CRS. This is consistent with what previous cross-sectional associations between CRS symptoms and general health-related QOL have suggested.³ This is also consistent with symptom domains that have been previously used to define general health-related QOL. For example, although our metric of general health-related QOL—the EQ-5D VAS—is unbiased in that it is not assessed based on any particular symptomatology, other measures of general health-related QOL are derived through assessments of symptoms, which include pain and energy level.^{12,32} Our findings further support the possibility that direct treatment of the extranasal symptoms of CRS, for example, pressure equalization tubes for ear pressure, may lead to significant improvements in QOL. Previous work examining

the clustering behavior of CRS symptomatology has also suggested independent pathophysiologic mechanisms that dominantly and separately control the severities of sleep and ear/facial discomfort symptoms.² Elucidation of these postulated pathophysiologic mechanisms also may serve to identify inflammatory pathways that could be therapeutically targeted for the greatest improvements in QOL. Finally, to what extent the nasal manifestations of CRS drive the extranasal manifestations such as poor sleep quality or ear or facial discomfort remain unclear. Nasal obstruction that occurs secondary to allergic rhinitis, another inflammatory disease affecting the nasal cavity, may directly contribute to sleep-disordered breathing.³³ A similar phenomenon may occur in CRS. Possibly patients suffering the greatest QOL decreases are those whose nasal symptoms are driving the extranasal symptoms (eg, poor sleep and ear or facial discomfort symptoms). Therefore, reduction in nasal disease manifestations (reflected by reduction of nasal symptoms) in some patients may directly lead to reductions in sleep and ear or facial pressure symptomatology and thereby maximally improve QOL. The improvement of sleep and ear/facial discomfort symptoms of CRS after endoscopic sinus surgery may be a reflection of this possibility.³⁴ Alternatively, endoscopic sinus surgery also may serve to reduce the load of inflammatory tissue as well as improve access for topical anti-inflammatory medications, which may ultimately serve as the dominant mechanisms for improvement of these extranasal symptoms. Clearly, teasing apart the complicated relationships between the nasal and extranasal manifestations of CRS requires further study. Our results nevertheless provide further evidence for the intriguing possibility that direct interventions targeting sleep quality and ear or facial discomfort may lead to the greatest improvements in general health-related QOL.

Acknowledgments

The authors gratefully acknowledge the contribution of the volunteers who participated in this study.

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