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Longitudinal improvement in nasal obstruction symptoms of chronic rhinosinusitis directly associates with improvement in mood

Marlene M. Speth[1] · Katie M. Phillips[2,3] · Lloyd P. Hoehle[4] · David S. Caradonna[2,5] · Stacey T. Gray[2,3] · Ahmad R. Sedaghat[6]

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Abstract

Purpose The effects of nasal obstruction in patients with chronic rhinosinusitis (CRS) are associated with depressed mood. We sought to validate this finding by determining whether improvement in nasal obstruction would translate to improvement in depressed mood.

Methods This was a prospective observational study of 150 patients undergoing medical management for CRS. Data were collected at two timepoints: enrollment and a subsequent follow-up visit 3–12 months later. Impact of nasal obstruction was measured using the Nasal Obstruction Symptom Evaluation (NOSE) instrument and depressed mood was measured using the 2-item Patient Health Questionnaire (PHQ-2). Sinonasal symptoms associated with CRS were also measured using the 22-item Sinonasal Outcome Test (SNOT-22). Clinical and demographic characteristics were collected. The relationship between changes in PHQ-2 and NOSE scores was determined with correlation and linear regression.

Results Change in PHQ-2 score was significantly correlated with change in NOSE score ($\rho = 0.30$, $p < 0.001$). After controlling for covariates, change in PHQ-2 score was associated with change in NOSE score (adjusted linear regression coefficient [β] = 0.014, 95% CI 0.006–0.022, $p = 0.001$). We confirmed these relationships, finding that change in PHQ-2 was associated (adjusted $\beta = 0.037$, 95% CI 0.013–0.061, $p = 0.003$) with change in the nasal subdomain score of the SNOT-22. Improvement in NOSE score by greater than 22 points was predictive of improvement in PHQ-2 score with sensitivity 54.5% and 83.8% specificity ($p < 0.001$).

Conclusion These results provide evidence that improvements in nasal manifestations/symptoms of CRS translate to significant improvements in mood.

Keywords Chronic rhinosinusitis · Nasal obstruction · Depressed mood · Outcomes

Introduction

Chronic rhinosinusitis (CRS) is an inflammatory disease of the sinonasal mucosa that is highly prevalent worldwide and associated with both decreased quality of life as well as lost productivity [1]. The pathophysiological mechanisms of CRS are heterogeneous and diverse, including allergy,

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✉ Ahmad R. Sedaghat
ahmad.sedaghat@uc.edu

[1] Klinik für Hals-, Nasen-, Ohren- Krankheiten, Hals-und Gesichtschirurgie, Kantonsspital Aarau, Aarau, Switzerland

[2] Department of Otolaryngology, Harvard Medical School, Boston, MA, USA

[3] Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, Boston, MA, USA

[4] Edward Via College of Osteopathic Medicine - Carolinas Campus, Spartanburg, SC, USA

[5] Division of Otolaryngology, Beth Israel Deaconess Medical Center, Boston, MA, USA

[6] Department of Otolaryngology, Head and Neck Surgery, University of Cincinnati College of Medicine, Medical Sciences Building Room 6410, 231 Albert Sabin Way, Cincinnati, OH 45267-0528, USA

immune dysfunction, and infection [2–4]. While CRS presents through multiple disease manifestations, which include acute rhinosinusitis exacerbations as well as exacerbations of comorbid pulmonary disease [5–8], the greatest impact of CRS is through the associated chronic symptomatology [1].

CRS is associated with both nasal and extranasal symptoms [9]. Previous work has shown that these symptoms of CRS are differentially associated with downstream consequences of functional impairments related to the disease. CRS is foremost perceived by patients by characteristic nasal symptoms, the most prominent of which is nasal obstruction [10–12]. Symptoms related to poor sleep quality or craniofacial discomfort are most associated with decreased quality of life [13–15]. Depressed mood in the setting of CRS has been most strongly associated with lost productivity [16].

Depression or depressed mood has been reported to be present in up to 40% of CRS patients and has been shown to be an important modulator of CRS outcomes [17]. Aside from the economic impact of lost productivity due to CRS [18], depressed mood also amplifies the quality-of-life detriment that is associated with CRS [19]. Multiple etiologies have been proposed for the depressed mood that has been associated with CRS. However, a conspicuous putative driver of depressed mood in CRS is the chronic nasal symptomatology that patients suffer from [20]. Nasal obstruction has been previously shown to be the most prominently perceived nasal symptom of CRS by patients [12]. Moreover, the impact of nasal obstruction in CRS patients has been shown to be directly associated with the degree of depressed mood experienced by those patients [21]. These findings suggest that the improvement of nasal obstruction in CRS may contribute to the improvement of depressed mood. To investigate this possibility, we performed a longitudinal study of medically managed CRS patients to determine if improvement of nasal obstruction would be associated with improvement in mood.

Materials and methods

Study participants

This study was approved by our institution's Human Studies Committee. A total of 150 patients (age 18 years or older) undergoing medical management for their CRS were recruited prospectively and provided informed consent for inclusion in this study. All participants met consensus guideline established criteria for CRS [22]. Patients with comorbid diagnosis of vasculitis, cystic fibrosis, sarcoidosis, immunodeficiency, and active CRS exacerbations (at enrollment or follow-up) were excluded from the study due to possible confounding effects. To remove confounding effects of heterogeneous treatments, endoscopic sinus surgery during the study period was also an exclusion criterion. Finally, although we did not exclude patients enrolled while on a psychotropic medication (anti-depressants or mood stabilizers), changes in psychotropic medications (e.g., change in the drug, dosage, or starting a new drug) during the study period constituted an exclusion criterion.

Study design and data collection

The study was designed as a prospective observational study and data was collected at two timepoints: enrollment and second at a clinical follow-up visit 3–12 months after enrollment. At enrollment, demographic and clinical characteristics of patients were collected, including information about age, sex, and smoking history. 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 [23–25]. During the time of treatment, patients were treated medically for CRS, which uniformly included intranasal saline irrigation, intranasal corticosteroids. Oral antibiotics or oral corticosteroids were given on a patient-by-patient basis, consistent with recommended guidelines for these medications [26].

Patient-reported outcome measures

All study participants completed three questionnaires at the time of enrollment and again at the clinical follow-up visit: the Nasal Obstruction Symptom Evaluation (NOSE) scale, which assesses the impact of nasal obstruction [27] and the 22-item Sinonasal Outcome Test (SNOT-22), which assesses CRS symptom burden [28]. The validated nasal, sleep, ear/facial discomfort and emotional subdomain scores of the SNOT-22 were also calculated as previously described [9]. All study participants were also assessed with the 2-item Patient Health Questionnaire (PHQ- 2) [29]. The PHQ-2 queries the frequency of anhedonia and feeling down, depressed, or hopeless over the prior 2 weeks. By assessing the two primary symptoms of major depressive disorder, the PHQ-2 may serve as a reflection of depressed mood and risk for clinical depression.

Statistical analysis

All analysis was performed using the statistical software package R (www.r-project.org). Correlations were calculated using Spearman correlation. Associations were sought using linear regression. A total of 150 participants were recruited to detect association between change in PHQ-2 score (as dependent variable) and change in NOSE score (as independent variable) while controlling for age, gender, smoking history, use of a psychotropic medication, comorbid asthma, allergy, polyps, and history of prior endoscopic sinus surgery

with medium effect size (Cohen's f2 = 0.15) with a power of 0.9 and at a significance level of 0.05.

Analysis of receiver operating characteristic (ROC) curves was performed with the pROC package [30]. The area under the ROC curve (AUC) was calculated with the trapezoid rule using the auc() function, and the 95% confidence interval (CI) of the AUC was calculated by performing 2000 bootstraps of the data with the ci() function. *P* value for significance of the ROC curve was determined by Wilcoxon rank-sum test.

Results

Study participants

A total of 150 participants (49.3% male and 50.7% female) were enrolled with a mean [standard deviation (SD)] age of 52.2 (15.6) years. Their clinical and demographic characteristics are summarized in Table 1. In addition, of all participants, 18.7% were on a psychotropic medication (antidepressant or mood stabilizer) at the time of enrollment. From enrollment to follow-up, the mean change in NOSE score was − 9.6 (SD: 24.0), mean change in PHQ-2 score was − 0.2 (SD: 1.2), and mean change in SNOT-22 score was − 6.6 (SD: 19.4). Out of the 150 participants, 125 experienced at least some change in NOSE score, while 56 experienced change in the PHQ-2 score. Of the 150 participants, 83 patients had a PHQ-2 score of zero at both enrollment and follow-up, suggesting no depressed mood at either timepoint. At enrollment 29 patients (19.3%) had PHQ-2 score greater than 1, while at follow-up, 24 patients (16.0%) had PHQ-2 score greater than 1.

Table 1 Clinical and demographic characteristics of study participants

	All study participants ($N = 150$)
Demographics	
Age, mean in years (SD)	52.2 (15.6)
Gender	
Male	49.3%
Female	50.7%
Smoking	28.0%
Comorbidities	
Aeroallergen hypersensitivity	48.7%
Aspirin sensitivity	8.7%
Asthma	44.7%
CRS characteristics	
Nasal polyps	56.0%
Previous sinus surgery	39.3%
Patient-reported outcome measures at enrollment	
NOSE, mean (SD)	38.3 (29.2)
PHQ-2, mean (SD)	0.7 (1.2)
SNOT-22, mean (SD)	35.1 (23.5)
Patient-reported outcome measures at follow-up	
NOSE, mean (SD)	28.7 (23.9)
PHQ-2, mean (SD)	0.5 (1.0)
SNOT-22, mean (SD)	26.9 (20.1)

Association of nasal obstruction with depressed mood

Previous work has shown that NOSE and PHQ-2 scores are correlated cross-sectionally [21]. We confirmed that NOSE score was correlated with PHQ-2 score at both enrollment ($\rho = 0.34$, $p < 0.001$) and follow-up ($\rho = 0.29$, $p < 0.001$). We also found that the change in NOSE score was correlated ($\rho = 0.30$, $p < 0.001$) with the change in PHQ-2 score (Fig. 1). Formalizing this relationship, the change in PHQ-2 score was associated with NOSE score on univariate ($\beta = 0.014$, 95% CI 0.007–0.022, $p < 0.001$) and multivariable ($\beta = 0.014$, 95% CI 0.006–0.022, $p = 0.001$) analyses which controlled for age, gender, smoking history, use of a psychotropic medication, comorbid asthma, allergy, polyps, and prior history of endoscopic sinus surgery. These associations between change in PHQ-2 score and change in NOSE score on univariate ($\beta = 0.021$, 95% CI 0.008–0.035, $p = 0.003$) and multivariable ($\beta = 0.021$, 95% CI 0.006–0.037, $p = 0.010$) analyses were even stronger in a subset analysis focusing on patients who had at least one non-zero PHQ-2 score at enrollment or follow-up (i.e., participants who experienced at least some depressed mood at enrollment or follow-up; we made the assumption that patients with PHQ-2 equal to zero at enrollment and at

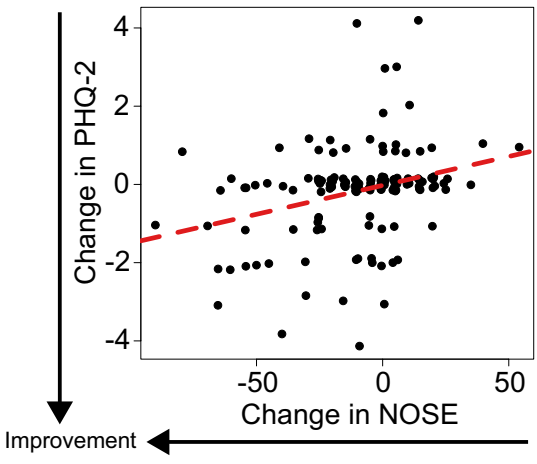

Fig. 1 Scatterplot of change in PHQ-2 score vs. change in NOSE score. Line of best fit is super-imposed as a dashed line

follow-up did not have any depressed mood that could be impacted by changes in nasal obstruction).

Finally, we also independently checked the relationship between depressed mood and nasal symptoms of CRS by comparing participants' PHQ-2 scores with nasal subdomain scores of the SNOT-22. The change in the PHQ-2 score was correlated ($\rho = 0.20$, $0 = 0.015$) with the change in the nasal subdomain scores (Fig. 2). The change in PHQ-2 score was associated with change in the SNOT-22 nasal subdomain score on univariate ($\beta = 0.036$, 95% CI 0.013–0.058, $p = 0.003$) and multivariable analyses ($\beta = 0.037$, 95% CI 0.013–0.061, $p = 0.003$).

Improvement in NOSE score is predictive of improvement in depressed mood

Although the minimal clinically important difference (MCID) of the PHQ-2 has not been established, using the formula of 0.5*standard deviation (at enrollment) for MCID, we can approximate the MCID of the PHQ-2 to be 0.6, which indicates that any improvement in the PHQ-2 (since PHQ-2 score changes only by integer values) would be deemed clinically important. We, therefore, tested whether change in NOSE score would be predictive of improvement in PHQ-2. We found that change in NOSE score could serve as a tool to detect patients experiencing improvement in PHQ-2 score (AUC = 0.730, 95% CI 0.632–0.828, $p < 0.001$). An improvement in NOSE score by greater than 22 points maximized the sum of sensitivity and specificity in identifying participants experiencing improvement in PHQ-2 score. Specifically, an improvement in NOSE score by greater than 22 points was predictive of participants experiencing at least one point improvement in PHQ-2 score with sensitivity 54.5% and 83.8% specificity.

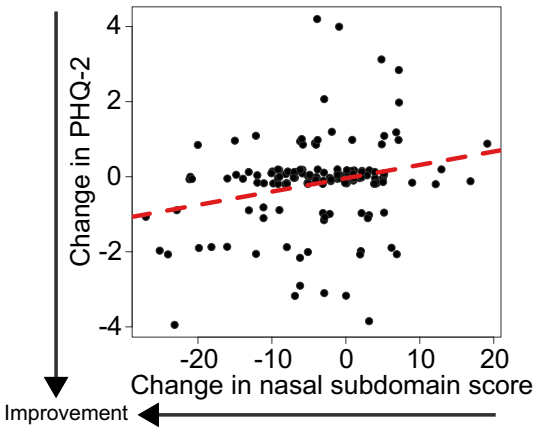

Fig. 2 Scatterplot of change in PHQ-2 score vs. change in SNOT-22 nasal subdomain score. Line of best fit is super-imposed as a dashed line

Subgroup analyses of association between improvement in NOSE score and improvement in depressed mood

To gain greater insights into the associations between improvement in NOSE score and improvement in depressed mood, we performed subgroup analyses to determine if this effect was observed more strongly in certain sub-populations of CRS patients. We found association between change in NOSE score and change in PHQ-2 in both participants with polyps ($\beta = 0.015$, 95% CI 0.006–0.024, $p = 0.002$) and without polyps ($\beta = 0.015$, 95% CI 0.001–0.029, $p = 0.036$). Stratifying participants by gender, there was likewise a significant association between change in NOSE score and change in PHQ-2 score for both men ($\beta = 0.017$, 95% CI 0.006–0.028, $p = 0.003$) and women ($\beta = 0.013$, 95% CI 0.002–0.023, $p = 0.022$). We similarly stratified participants based on comorbid asthma, comorbid allergy, and previous sinus surgery, and in all cases, we found statistically significant association between change in NOSE score and change in PHQ-2 score regardless of stratification and strata. When stratifying patients by smoking status, we found that a statistically significant association between change in NOSE score and change in PHQ-2 score for non-smokers ($\beta = 0.020$, 95% CI 0.010–0.030, $p < 0.001$), but not smokers ($\beta = 0.003$, 95% CI − 0.007–0.015, $p = 0.525$), although there were only 40 participants with a history of smoking.

Discussion

Previous studies have demonstrated a strong association between inflammatory sinonasal disorders, such as allergic rhinitis or CRS, and depressive disorders [31–33]. Depressed mood may be present in up to 40% of patients with CRS and has manifold effects on the CRS disease course [17, 31, 34]. Depressed mood is an important modulator of CRS on quality of life, being associated with worse quality of life, worse outcomes after treatment and greater CRS-related productivity loss [16, 19, 35]. Previous work has suggested through cross-sectional association that the nasal symptoms of CRS could be important drivers of depressed mood [21]. In this study, we sought to support this possibility by longitudinally studying a cohort of medically managed CRS patients to investigate the responsiveness of mood to changes in nasal symptoms with a focus on nasal obstruction. We confirmed and extended those prior findings by showing that improvements in nasal obstruction were directly associated with improvements in depressed mood, with improvements in NOSE score by more than 22 points being a specific predictor of clinically significant improvement in mood.

Various mechanisms have been proposed to explain how CRS may induce depressed mood. Psychosocial stress, for

example, due to social and interpersonal problems from the effects of chronic sinonasal symptomatology may lead to or exacerbate depressed mood. In addition, depression has long been associated with systemic inflammation [36]. The effect of inflammatory mediators on the central nervous system to induce a depression-like syndrome, characterized by symptoms such as fatigue and loss of appetite, has been referred to as "sickness behavior" [37]. It is possible that sickness behavior may be promoted in the setting of CRS by inflammatory mediators produced in the paranasal sinuses potentially acting directly on the central nervous system, either locally through the skull base or through systemic circulation, to induce depressed mood.

In this study, we found that the improvement in the nasal symptoms of CRS is associated with the improvement of depressed mood and that improvement in nasal obstruction was predictive of clinically significant improvement in depressed mood. Our results are potentially consistent with any of the above mechanisms for the impact of CRS on mood. The nasal symptoms of CRS, in particular nasal obstruction, have been shown to be the primary—if not only—disease manifestation that patients perceive and focus on [10, 12]. It would make sense that alleviation of nasal obstruction and nasal symptoms of CRS after treatment would concomitantly alleviate psychosocial stress from the disease as well. The burden of nasal symptoms has also been shown to be reflective of objective measures for the severity of CRS [38–40]. It is possible that the improvement of nasal symptoms of CRS may be a reflection of the objective inflammatory disease burden that drives depressed mood.

It is important to note that the treatment of CRS does not uniformly lead to the improvement of depressed mood. In our cohort, over half of the participants did not have any evidence of depressed mood at both enrollment and follow-up. As over half of CRS patients may not be afflicted by depressed mood, the improvement of nasal symptoms would not be expected to improve mood in these patients. Moreover, there may certainly be non-rhinologic causes for depressed mood that may not respond to treatment of CRS. This may explain why in some cohorts treatment of CRS to improve nasal symptoms [41] improves depressed mood [42, 43] but not in other cohorts [44].

The results of our study should be interpreted in the context of its limitations. The distinction between depressed mood and depression (i.e., major depressive disorder) is important. Depression is a formal diagnosis, while depressed mood is a symptom that may be reflective of not only depression but other diagnoses such as dysthymia or may even be a natural reaction that patients may experience in response to life stressors. The PHQ-2 has been used as a screening tool for depression, but it is also assesses depressed mood as a reflection of sadness and anhedonia. Our study more accurately is a reflection of depressed mood and we cannot draw any conclusions about an underlying reason (e.g., depression vs. dysthymia vs. normal reaction). As noted above, because most CRS patients do not have comorbidly depressed mood, our results are not generalizable to the entire CRS patient population. Specifically, in our cohort, only 67 out 150 patients had non-zero PHQ-2 score at either study timepoint. Association, which we detect here, does not decisively provide directionality—in other words, does change in nasal obstruction symptoms lead to change in depressed mood or does change in depressed mood lead to change in nasal obstruction symptoms? Although both possibilities are feasible, the only intervention applied to patients in this study was treatment for nasal symptoms through medical management of CRS consisting of intranasal saline irrigation and intranasal corticosteroids. It is, therefore, unlikely that the medical treatment of CRS would have a primary mechanism to improve depressed mood, which would then lead to improved reporting of nasal symptoms. By contrast, it is much more likely that the treatment of CRS through intranasal medications would improve nasal obstruction symptoms, which would then lead to improvement in mood. Finally, although none of our patients had any change in psychotropic medication over the study period, we cannot exclude the possibility of other factors, e.g., psychosocial stressors, that may have confounded participants' moods. That we have nevertheless found an association between improvement of nasal symptoms of CRS and depressed mood suggests that the underlying relationship, the exact nature of which requires further elucidation, is strong enough to be detected despite possible confounders.

Conclusion

Medical management of CRS, with its targeted delivery to the sinonasal cavity, leads to improvement in both nasal obstruction and concomitant improvement of depressed mood. The improvement of nasal obstruction symptoms is associated with improvement in depressed mood. These results demonstrate the direct impact that nasal symptoms of CRS may have on patient mood.

Compliance with ethical standards

Conflict of interest There are no potential conflicts or financial relationships.

Ethical approval This study and its design were approved by the institutional human studies committee.

Informed consent All patients provided informed consent.

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