

Olfactory Dysfunction and Chronic Rhinosinusitis



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KEYWORDS

• Olfaction • Chronic rhinosinusitis • Olfactory loss • Olfactory dysfunction

KEY POINTS

- The overall prevalence of olfactory dysfunction in patients with chronic rhinosinusitis (CRS) is high and imparts significant impact on patient quality of life.
- Olfactory dysfunction is caused by a combination of physical obstruction of odorant molecules to the olfactory cleft and an inflammatory response of the olfactory epithelium.
- Both subjective and objective measures of olfaction are important for clinicians managing patients with CRS.
- Oral steroids and endoscopic sinus surgery are associated with posttreatment improvements in olfactory dysfunction for patients with CRS with nasal polyposis.

INTRODUCTION

Chronic rhinosinusitis (CRS) is a common disease affecting 12% of the population of western countries¹ and a leading cause of olfactory dysfunction in the general population.² It is estimated that from 60% to 80% of patients with CRS have some form of olfactory impairment, which is 1 of the 4 cardinal symptoms of CRS.^{3–5} Although olfaction plays an important role in quality of life (QOL) and safety functions for patients, only recently has there been an increasing focus of clinicians and researchers alike on olfactory dysfunction in patients with CRS. This review first aims to summarize and review the epidemiology and risk factors of olfactory dysfunction in CRS. Then, the pathophysiology, clinical features, and differences between patients with CRS with nasal polyposis (CRSwNP) and patients with CRS without nasal polyposis (CRSSNP) are reviewed. Next, the authors describe both subjective and objective measures used to assess olfaction as well as the impact of olfactory dysfunction in CRS on QOL. Finally, the authors review the impact of both medical and surgical management of olfactory dysfunction in CRS.

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Immunol Allergy Clin N Am 40 (2020) 223–232

<https://doi.org/10.1016/j.iac.2019.12.013>

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EPIDEMIOLOGY

CRS is defined by both subjective and objective criteria, with a subjective change in the sense of smell as 1 of the 4 defining symptoms.^{1,6} In general, olfactory dysfunction can be classified as either qualitative or quantitative. Qualitative measures include phantosmias, dysosmias, parosmias, and agnosias. Qualitative dysfunction are somewhat rare manifestations in CRS, but have been reported.² Reden and colleagues² reported 7% of 392 patients with CRS having some form of phantosmia or parosmia. However, quantitative measures of olfaction, which identify hyposmia and anosmia, are more commonly affected in patients in CRS, with 60% to 80% of patients with CRS overall reporting some form of olfactory dysfunction.²⁻⁴ In a recent metaanalysis reviewing objective measures of olfaction in the CRS population, the overall prevalence of olfactory dysfunction was found to be 67% using the 40-item smell identification test (SIT-40), and 78% using the total Sniffin' Sticks score.⁷ Interestingly, up to one-fourth of patients with olfactory loss may not recognize their loss, which is hypothesized to be secondary to a prolonged gradual decline in loss of smell.⁸

Although often overlooked, olfactory dysfunction can have potentially dire consequences for patients, including environmental and safety-related risks, impaired nutritional status, and decreased QOL. Pinto and colleagues⁹ demonstrated that older, anosmic patients had a 3-fold increased odds ratio of death compared with normosmic patients, even when controlled for chronic diseases, and that olfactory function was one of the strongest predictors of 5-year mortality. The association between smell loss and depression is also well documented.¹⁰ Similarly, and presumably interrelated, there is also a well-established correlation between CRS and depression. It is estimated that from 11% to 40% of CRS patients have depression.¹¹ Other studies have specifically evaluated the relationship among olfactory dysfunction, CRS, and depression.¹²

In addition to disruptions in the ability to smell, the sense of taste also appears to be impaired in patients with CRS and should be considered when evaluating olfaction in patients with CRS. A recent prospective investigation demonstrated dysgeusia in 28% of a CRS patient population.¹³ Moreover, impaired flavor identification also appears to be a strong predictor for QOL, life satisfaction, depressive symptoms, and health assessment in patients with CRS.¹⁴ Nonetheless, orthonasal olfactory dysfunction has also been shown to directly correlate with poor eating-related QOL,^{15,16} and the role of retronasal olfaction in the perception of food may also be implicated.^{17,18} Overall, the importance of chemosensory dysfunction in patients with CRS should not be overlooked given its critical importance for the enjoyment of food and the socially shared experience of eating.

RISK FACTORS FOR OLFACTORY DYSFUNCTION IN CHRONIC RHINOSINUSITIS PATIENTS

CRS is multifactorial in nature, although the exact pathophysiology is not completely understood. As one of the hallmark symptoms of the disease, olfactory dysfunction is currently thought to be a manifestation of an immense inflammatory response. Specific, independent risks factors for olfactory dysfunction in CRS include a comorbid diagnosis of smoking, nasal polyposis, and asthma.¹⁹

Patients with CRSwNP have several potential risk factors and mechanisms of olfactory dysfunction. First, physical obstruction of the olfactory cleft by nasal polyps is an intuitive risk factor for impaired olfaction. In addition to mechanical obstruction, increased tissue eosinophilia appears to have a local, damaging impact by release cytotoxic substances to the olfactory neuroepithelium.²⁰ Moreover, systemic eosinophilia in

patients with CRSwNP and comorbid asthma appears to impart an increased overall systemic inflammatory response, which also affects the olfactory cleft.

Alternatively, patients with CRSsNP also present with olfactory dysfunction, although the overall prevalence and severity of disruption of olfaction in these patients may be less than those patients with CRSwNP.²¹ Lower rates of olfactory dysfunction in patients with CRSsNP may be secondary to a less robust inflammatory response and lack of obstructive polyps of the olfactory cleft. Although most CRSsNP patients have subjective olfactory dysfunction, only 17% were found to have objective olfactory dysfunction.¹⁹ These patients are typically less responsive to medical and surgical therapy.²²

PATHOPHYSIOLOGY OF OLFACTORY DYSFUNCTION IN CHRONIC RHINOSINUSITIS

The 2 leading theories of the pathogenesis of olfactory dysfunction in patients with CRS include, first, a conductive loss, limiting the ability of odorants to present to the olfactory cleft, and second, an inflammatory reaction near the olfactory cleft leading to decreased transmission to olfactory neurons, and a resultant decrease in size of the olfactory bulb.²³ It is likely that both theories play a role in olfactory dysfunction in CRS.

Chronic inflammation of the olfactory cleft may lead to damage to the olfactory epithelium via olfactory sensory neuron apoptosis, leading to the loss of sensory neurons.²⁴ Chronic inflammation may potentially inhibit olfactory neurogenesis and thus poor recovery of the neuroepithelium, ultimately leading to a transition of this specialized neuroepithelium to squamous or respiratory epithelium.²⁵ However, this does not explain entirely how inflammation leads to olfactory loss. Clinically, patients may have fluctuating olfactory loss that may be transiently reversed with systemic corticosteroids.²⁶ There are specific inflammatory mediators that may play a role in the temporary loss of smell associated with CRS. Eosinophils and its inflammatory cytokines (interleukin-2 [IL-2], IL-5, IL-6, IL-10, and IL-13) have been implicated in olfactory loss in CRS.²⁷ It is hypothesized that perturbations in this cytokine milieu may affect the intracellular tumor necrosis factor- α /c-Jun-N-terminal kinases pathway. Activation of this pathway effects neuronal function and may lead to apoptosis and cell death, and inhibition of this pathway may have neuroprotective effects.²⁸

In addition to inflammatory-related issues, investigators have demonstrated an inverse relationship between CRS severity and olfactory bulb size. Chronic sensory deprivation of olfactory neurons appears to be associated with a decrease in function and decrease in size of the olfactory bulb.²⁹ Similar findings have been reported in patients with postviral anosmia.³⁰ However, it is unclear if olfactory bulb volume is a consequence or cause of olfactory dysfunction.

SUBJECTIVE MEASURES OF OLFACTORY DYSFUNCTION IN CHRONIC RHINOSINUSITIS

The first step in measurement of olfactory dysfunction in patients with CRS is a subjective assessment. Subjective measures of smell loss may range from limited assessments such as those found as single items in the sinonasal outcome test (SNOT-22) and rhinosinusitis disability index to more sophisticated, olfactory-specific, QOL measures, such as the questionnaire of olfactory disorders-negative statements (QOD-NS).³¹

Although the SNOT-22 questionnaire is the gold standard used to describe sinonasal QOL in patients with CRS, this survey has a single item dedicated to olfactory (and taste) function. The use of a single item limits the ability to identify varying degrees of olfactory dysfunction. In order to provide a more sensitive and detailed assessment, the QOD has been validated and shows good internal consistency and test-retest

reliability.³² This olfactory-specific questionnaire and its abbreviated version, the QOD-NS, delineate subjective olfaction and can be used to assess the impact of olfactory loss and measure the impact of therapeutic interventions.¹² Despite the critical importance of subjective measures in patient QOL, caution should be used in using subjective olfaction metrics alone because subjective assessments may have poor correlation with objective measures of olfaction.^{23,33,34}

OBJECTIVE MEASURES OF OLFACTORY DYSFUNCTION IN CHRONIC RHINOSINUSITIS

Objective olfactory function can be grouped into 3 general categories, including psychophysical assessments, imaging modalities, and electrophysiologic tests. In the setting of CRS, psychophysical tests are the most commonly used and readily accessible. Although imaging is also readily accessible, electrophysiologic testing is generally reserved for academic purposes.³⁵

There are more than 20 objective psychophysical smell identification tests described in the literature.²³ However, traditionally in the United States, the 40-item SIT-40, also known as the UPSIT, is the most commonly used validated objective measure of olfactory loss. SIT-40 was introduced at the University of Pennsylvania by Doty and colleagues³⁶ in 1984, which includes a booklet of 40 scratch-and-sniff items, from which a patient has to choose from 1 of 4 proposed smells in a multiple-choice format. This final score is normalized over age. In Europe, and increasingly in the United States, the Sniffin' Sticks test is more commonly used. This test battery assesses odor threshold (T), odor discrimination (D), and odor identification (I), as well as a composite "threshold-discrimination-identification" (TDI) score by using 16 different odorant-containing pens.^{37,38} This system also normalizes for gender and age in order to give a more accurate assessment of olfaction. Both of these measures have been used to evaluate olfactory loss in CRS patients. A recent metaanalysis of olfactory function in patients with CRS demonstrated average SIT-40 and TDI scores in the moderate hyposmia range.⁷

Olfactory function can be assessed both orthonasally and retronasally. Orthonasal olfaction is the process in which olfaction is most commonly discussed, with an odorant passing from anterior to posterior from the air, through the nose to the olfactory mucosa. Retronasal olfaction, however, occurs when odorants move from the oral cavity to the nasal cavity through the nasopharynx and to the olfactory mucosa. Retronasal olfactory testing is performed by presenting odorized powders to the oral cavity. Although patients with CRSwNP may have increased retronasal olfaction as compared with traditional orthonasal measures, retronasal olfaction is diminished across patients with CRS.³⁹

Beyond psychophysical assessments, imaging of the olfactory cleft and the olfactory bulb can be helpful diagnostic tools to assess olfactory dysfunction in CRS. Computed tomography (CT) imaging is traditionally used to assess the degree of sinonasal mucosal inflammation in patients with CRS. Recent reports have demonstrated that the degree of radiologic opacification in the olfactory cleft on CT correlates with the degree of olfactory loss in CRS.⁴⁰ This correlation was stronger in patients with CRSwNP compared with patients with CRSsNP. In line with this, the olfactory cleft endoscopy scale is a validated endoscopic scoring system shown to reliably correlate with objective olfactory function that can easily be performed in routine evaluations for patients with CRS.⁴¹

MRI is also a useful tool in evaluating patients with olfactory loss and CRS. It can provide detailed imaging of the olfactory apparatus, which includes the olfactory bulb, olfactory tract, sulcus, and the central olfactory projection areas. There is evidence that olfactory bulb size on MRI correlated with olfactory loss in patients with

CRS.²⁹ There is also evidence of olfactory bulb plasticity, demonstrated by changes in size of the olfactory bulb in accordance with the current olfactory status in patients with CRS.⁴² Gudziol and colleagues⁴² found that patients with CRSwNP undergoing endoscopic sinus surgery (ESS) had objectively improved olfaction and postoperative increase in olfactory bulb volume size.

OUTCOMES IN OLFACTION AFTER MEDICAL THERAPY

Medical treatment plays an important role in the overall CRS treatment algorithm. Many studies have demonstrated the utility of medical therapy in improving disease severity, overall QOL measures, as well as the utility of medical therapy in improving olfactory outcomes in patients with CRS. Herein, the authors discuss specific olfactory outcomes following various medication therapies, including antibiotics, oral steroids, topical steroids, and combined oral and topical steroids. Most of these studies specifically evaluated patients CRS with polyposis.

The metaanalysis of Banglawala and colleagues⁴³ of randomized controlled trials (RCTs) specifically evaluating olfactory outcomes after oral steroid treatment in patients with CRSwNP pooled 4 RCTs and found that all studies showed a subjective improvement in olfaction compared with placebo.^{44–47} With follow-up limited to a maximum of 6 months, durability of response could not be assessed. Meanwhile, 2 RCTs evaluating objective olfactory outcomes after oral steroids demonstrated short-term improvement with a 2-week follow-up.⁴⁵ Emerging evidence also suggests that the degree of olfactory response following the use of oral glucocorticoids correlates with the degree of olfactory improvement following ESS.⁴⁸ Although improvements in olfaction following oral steroid administration are certain, the long-term efficacy and sustainability of response are less clear.

Topical steroids may also play a role in the medical management of olfactory dysfunction in CRS. In the metaanalysis by Banglawala and colleagues,⁴³ 12 RCTs specifically evaluated olfactory outcomes after various topical steroid use in CRS patients. These studies evaluated various forms of topical steroids, including fluticasone, budesonide, and mometasone compared with placebo. These investigators found there was overall subjective improvement in subjective measures, but no objective improvement. As such, it is unclear if the use of topical steroids alone for patients with CRS improves olfactory outcomes, especially given the possible poor correlation between subjective and objective measures.

Meanwhile, 5 clinical trials evaluated the combination of both oral and topical steroids compared with placebo to assess olfaction in CRS patients.⁴³ In the 5 studies, patients received oral prednisolone for 2 weeks followed by various durations of topical steroid sprays. One-half of the subgroups showed statistical improvement in subjective olfaction, whereas 1 of 3 subgroups demonstrated improvement in objective olfaction.

The use of monoclonal antibodies for patients with CRSwNP may also improve olfactory function.^{49,50} Presumably these treatments reduce overall polyposis burden throughout the sinonasal cavities, including the olfactory cleft. Emerging evidence from the postinfectious olfactory loss literature suggests that intranasal sodium citrate may promote improvements in olfaction; however, further investigation is needed to fully elucidate the effects of intranasal sodium citrate, especially as it applied to the CRS patient population.³⁵

There have been various other medical treatments to assess olfactory dysfunction in CRS patients that have been studied in the literature, including antibiotics, antifungals, and immune modulators. Although doxycycline and azithromycin may have anti-inflammatory properties, investigations with both of these medications found no significant improvement in olfaction after treatment compared with

placebo.^{51,52} Similarly, an investigation of intranasal amphotericin B for 3 months compared with placebo also failed to detect an improvement in posttreatment olfaction.⁵³

Although there is much literature evaluating olfactory outcomes after medical therapy in CRSwNP patients, there is significantly less available literature specifically investigating patients with CRSsNP. There is some evidence that oral steroids in combination with antibiotics and nasal steroids improve symptoms of CRS, including olfaction with short-term follow-up.⁵⁴ However, only 1 of these studies specifically examined olfactory outcomes as the primary endpoint.⁵⁴ Other than steroids, low-dose macrolide therapy can be used for CRSsNP patients. It is hypothesized that the potentially anti-inflammatory effects of the antibiotic may reduce inflammation. However, Videler and colleagues⁵¹ found no significant difference in objective smell testing after 11 weeks of low-dose macrolide therapy.

It can be concluded that, although many medical treatments have been shown to have some efficacy in the treatment of CRSwNP, only oral steroids have been shown consistently to improve short-term olfactory outcomes. Evidence is lacking, however, for CRSsNP patients. Long-term outcomes need to be further studied.

OUTCOMES IN OLFACTION AFTER SURGICAL THERAPY

There has been ample research evaluating olfactory outcomes after ESS for CRS. However, one must be cautious in interpreting the data for olfactory outcomes because most studies do not define the extent of surgery.

Objective olfactory function on objective testing generally improves following ESS, with the potential for most significant improvements in women, patients with significant nasal polyposis, and patients with aspirin intolerance.^{55,56} Moreover, in a study that specifically evaluated factors associated with recovery of olfactory function after ESS for CRS, patients with more dramatic preoperative loss were more likely to regain postoperative olfactory function in the form of improved UPSIT scores.¹⁹ This study also demonstrated more dramatic olfactory improvement in patients with CRSwNP as compared with patients with CRSsNP after ESS.

One of the first studies to specifically evaluate olfactory-specific QOL outcomes in CRS was published by Soler and colleagues³¹ and demonstrated a significant improvement in postoperative QOD-NS scores. Moreover, in this study, baseline radiologic scores predicted postoperative changes in QOD-NS scores. Now, with a growing interest and body of literature examining olfactory-specific outcomes after ESS, a recent metaanalysis evaluated 24 studies on this topic.⁵⁷ This review demonstrates postoperative improvements in measures of olfaction in 23 out of the 24 studies, with either objective or subjective testing. Although 50% of nearly 1500 patients reported some improvement in olfaction, several studies did report some degree of worsening of olfaction after ESS.

In addition to ESS alone, there have been studies that specifically evaluated olfactory outcomes after septoplasty and septorhinoplasty for nasal obstruction. In theory, a septoplasty can potentially improve access for odorant molecules to the olfactory cleft. The studies show there is at least short-term improvement in objective olfactory outcomes.^{58,59} It is unclear, however, if adding septoplasty to ESS compared with ESS alone improves olfactory outcomes in the CRS population.

Overall, ESS for CRS patients may have a potential benefit in improving olfaction in a subset of patients, including those with nasal polyposis and anosmia. ESS should be performed within established guidelines.

Finally, comparisons between medical and surgical management of CRS have yet to be fully elucidated, but a prospective, multi-institutional study by DeConde and

colleagues⁶⁰ examined this comparison in 281 medically refractory CRS patients who were candidates for ESS. In this study, 20% of patients elected to continue medical management, whereas 80% chose to undergo ESS. Both groups experienced statistically significant improvement in objective testing for olfactory dysfunction, whereas prior ESS was the only risk factor associated with failure of postoperative olfaction.

SUMMARY AND FUTURE CONSIDERATIONS

Olfactory dysfunction is highly prevalent in the CRS population. This finding is likely related to both an obstructive and an inflammatory response in the olfactory cleft. However, the fluctuating nature of olfactory loss in CRS is still not completely understood. Understanding the importance of inflammatory mediators and their downstream effects in the olfactory epithelium can lead to future targeted therapies, such as stem cell therapy,⁶¹ or even novel treatment strategies, such as electrical stimulation of the olfactory epithelium.⁶² Currently, oral steroids and ESS have both demonstrated some degree of efficacy in improving olfactory dysfunction in the short term, especially in patients with CRSwNP; however, durability of response of these therapies remains unclear.

The QOL impacts of olfactory dysfunction in patients with CRS are increasingly understood and are paramount to this patient population. Both validated objective and subjective assessments of olfaction should be performed in patients with CRS. Given the increasing recognition of the role of taste and flavor in QOL, measures of gustation should be considered in future investigations.

DISCLOSURE STATEMENT

The authors have nothing to disclose.

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