Review Article

Chronic rhinosinusitis and endoscopic sinus surgery

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Abstract Olfactory dysfunction is a major symptom reported by patients with chronic rhinosinusitis (CRS). Surgical treatment of this disease requires close surveillance of such dysfunction because of wide ranging implications for safety, quality of life, and impact on the flavor of foods and beverages. This review highlights key findings regarding the influences of endoscopic sinus surgery (ESS) on olfactory function across the unique presentations of CRS. Such findings provide information useful for informing patients of potential complications and for obtaining informed consent prior to surgical intervention. ESS has been shown to improve olfaction across all types of CRS as assessed through quantitative testing and subjective reports. The presence of nasal polyposis (NP) and eosinophilia have been identified as predictors of significant postoperative olfactory improvement. When indicated, judicious partial resection of the middle turbinate may result in improved olfactory function without a risk of long term complication. Careful attention to the olfactory cleft and frontal sinus recess are important in limiting olfactory complications by avoiding indiscriminate disruption of olfactory epithelium. Given the chronic nature of the disease, surveillance of olfactory function in patients with CRS is a lifelong activity that will evolve as emerging technologies become available.

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Introduction

Olfactory dysfunction is a well-established cardinal symptom of chronic rhinosinusitis (CRS), with prevalence estimates ranging from 30% to 80%.1 Although this wide range of estimates undoubtedly reflects variability in testing, the skill of the surgeon, underlying disease, and other factors, even the lowest of these estimates is high. This underscores the importance of addressing this issue when considering surgical interventions, particularly given the impact of olfactory dysfunction on quality of life and safety. The pathophysiology of olfactory dysfunction in CRS is multifactorial, involving significant obstructive and sensorineural processes.2,3 Obstructive pathology causing conductive loss includes nasal polyposis, mucosal edema, adhesions, and septal deviations. Sensorineural loss is expectedly more complex with identification of inflammatory factors, neural involvement of the olfactory epithelium, and comorbid skull base disease.

This article describes the impact of ESS on olfactory function across the unique phenotypes of chronic rhinosinusitis. Evidence documenting functional outcomes of olfactory ability after ESS is summarized as guidance for discussing patient expectations. In addition, we review intraoperative practices and measures that reduce the likelihood of iatrogenic olfactory loss.

Anatomy and physiology of olfaction

This section is not intended to be a compendium on olfactory anatomy pathway. However, a working knowledge of relevant sinonasal and skull base anatomy, along with an understanding of pathophysiologic pathways involved, is essential in tailoring surgical goals to limit iatrogenic olfactory dysfunction and improve postoperative olfactory outcomes. Olfaction starts with inhalation of odorant stimuli. There are two peripheral pathways involved in the physical transport of odorants to olfactory cleft: orthonasal flow of odorous stimuli directly through the nares and retronasal flow via the choanae. The retronasal pathway is involved in perception and refinement of flavor during consumption of solid and liquid food.5 The olfactory cleft epithelium consists of 10–20 million olfactory neurons. Histologically, this epithelium is pseudostratified columnar and includes basal cells (stem cells), supporting cells (Bowman glands, microvilli cells, sustentacular cells) and olfactory receptor cells.2,7

The receptor cells are bipolar cells with nonmotile ciliated dendrites that extend from the olfactory vesicle to epithelial/apical surface for detection of odor stimuli of odorous stimuli and a central portion connected to the olfactory bulb without an intervening synapse in the receptor cells. When odorants reach the cleft, diffusion through a mucous layer covering the receptor cells occurs. Odorants are presented to the receptor cells via odorant-binding proteins. This results in activation of G proteins, and cyclic adenosine monophosphate-mediated depolarization of the olfactory neuron with subsequent action potential.

The signal is then transmitted along unmyelinated olfactory sensory neuron axons which make up cranial nerve I. Axons from the olfactory neurons form nerve bundles (filia olfactoria), cross the cribriform plate superiority through approximately 20 foramina, and synapse with other neurons in the olfactory bulb. These second order neurons then transmit the signal to the piriform cortex, olfactory nucleus and tubercle, amygdala, and entorhinal cortex. Some inhaled chemicals can be detected by elements of the trigeminal nerve within the olfactory mucosa and throughout the nasal epithelium, as well as by afferents located in the back of the mouth and throat (e.g., via the glossopharyngeal and vagus nerves). However, these routes do not produce olfactory sensations and are beyond the scope of the present review.

Intranasal extensions of the olfactory epithelium extend about 1 cm inferiorly onto the nasal septum. From a sagittal perspective, the olfactory epithelium extends about 2 cm in length on both sides along the superior-posterior septum with potential extensions posteriorly to the face of the sphenoid sinus, and laterally to the superior and middle turbinates.3,4

Olfactory loss in chronic rhinosinusitis

Identification of specific etiology factors driving olfactory dysfunction in CRS is an evolving topic in the context of multiple phenotypes. However, it is widely recognized that loss is multifactorial with conductive and sensorineural mechanisms. Conductive loss may be seen in patients with structural pathologies preventing optimal transport of odorants to the olfactory cleft. These include nasal polyposis, mucosal edema, and nasal lesions.7,8 Sensorineural loss may be mediated by inflammatory changes to the neurepithelium, as demonstrated in histologic studies and from response to corticosteroids.9,10 Additional significant risk factors that predict presence of olfactory dysfunction in CRS patients include tobacco smoking, age over 65 years, and asthma.11

Multiple studies employing heterogenous methodologies have investigated the prevalence of olfactory dysfunction in CRS, with mean scores typically falling in the hyposmic range.1,11,12 The wide range in reported prevalence reflects variability in CRS subtypes, where by those CRS patients with nasal polyps(CRSwNP) evidencing a higher level of olfactory impairment. Variability in testing may also contribute to the heterogeneity of observations. For example, shorter tests, such as the 12-item Brief Smell Identification Test (B-SIT), or subcomponents of larger tests, such as the threshold component of the Sniffin’ Sticks test, may underestimate the degree of impairment across subgroups, although evidence for this is weak.1,12–14 In a meta-analysis evaluating prevalence and patient specific factors, Kohli et al12 noted that patients with CRSwNP had a higher degree of olfactory impairment at baseline than CRS patients with mixed phenotypes. In addition, worse scores from opacification of the olfactory cleft on computed tomography (CT) imaging, and eosinophilic CRS appear to be significant factors that predict olfactory impairment.15–17 These findings and risk factors should be discussed when considering patients for ESS.

Olfactory outcomes following endoscopic sinus surgery

Improvement in quality of life of patients undergoing endoscopic sinus surgery is well documented.18 However,
isolating information regarding olfactory improvement from these studies have provided inconsistent results. A cursory review of several small studies reveals improvement ranging from 25% to 100% of the subjects, providing conflicting information for counseling patients.\textsuperscript{12} Isolating information regarding olfactory improvement from these studies have provided inconsistent results. It would be simplistic to provide a number, or probability when predicting olfactory improvement from ESS. Notably, this is a challenging topic given the heterogeneity of study methodologies, mixed endo- and phenotypes of CRS, poor reliability of subjective olfaction assessment, and diversity in quality of life tools addressing chemosensory function. In addition, multiple quality of life studies addressing outcomes following ESS tend to mix olfaction status with other outcomes rather than isolate improvement in olfaction as primary endpoint. Of note, Kohli et al\textsuperscript{12} conducted a systematic review and a meta-analysis of original research studies addressing the impact of ESS on olfaction patients CRS on the basis of aggregated olfactory data. They reviewed studies from widely available databases up to October 2015 that reported subjective or objective olfactory data in chronic rhinosinusitis patients pre- and post-ESS. Studies reporting outcomes of subjective olfaction utilized the visual analog scale and response to question 21 of the Sinonasal Outcome Test. Olfaction was quantitatively addressed using the Brief Smell Identification Test, the 40-item Smell Identification Test, and the Sniffin’ Sticks Test. The latter included a smell threshold, discrimination, and identification (“TDI”) score. The meta-analysis found that there is an overall postoperative improvement in olfaction in patients undergoing ESS. Improvement was found in both hyposmics and anosmic patients, a finding that contrasts with other studies reporting significant improvement in only anosmics.\textsuperscript{13}

Across all forms of testing included in the studies of the meta-analysis, the CRSwNP patients evidenced greater olfactory improvement following ESS. A negative correlation between nasal polyposis and baseline olfaction has previously been reported.\textsuperscript{13,19} However, the increased surgical responsiveness in CRSwNP cohorts may be driven by elimination of the physical barrier preventing odorous stimulants from reaching the olfactory cleft and superior turbinate in patients with CRS.\textsuperscript{12,13,20} In addition, since continued presence increases the risk of postoperative inflammation, it is acceptable to expect and to advise that CRSwNP patients have a higher likelihood of achieving significant olfactory improvement following ESS.

The mechanism of reversing any present sensorineural loss any patient with CRS with or without polypsis not well understood. However, biopsies of nasal mucosa from the olfactory cleft and superior turbinate in patients with CRS exhibit inflammatory cells and changes in architecture with expected negative impact on neuronal function.\textsuperscript{10,21} Furthermore, multiple studies have shown that patients with a higher degree of opacification of the olfactory cleft, with and without polyposis, have a higher degree of preoperative loss and less improvement in olfaction following surgery.\textsuperscript{12,22} Such observations suggest that inflammation within the mucosa of the olfactory cleft may cause irreversible changes that limit postoperative improvement in olfaction following ESS. Unfortunately, this is a difficult subject to study in large populations given the heterogeneity of CRS phenotypes, evolving knowledge about inflammatory changes in CRS at cellular level, and concern of precipitating iatrogenic anosmia from disruption of the mucosa within the olfactory region.

**Intraoperative considerations**

The preservation of functional structures and mucosa is a key tenet in ESS. Impaired olfaction is not unexpected in postoperative endonasal endoscopic anterior skull base surgery involving removal or disruption of the olfactory bulb. However, in ESS addressing sinonasal disease, the classic teaching is to avoid unnecessary dissection and exercise great caution in certain areas that may contain olfactory epithelium. These would include the olfactory cleft, the superior posterior septum, the middle turbinate, and the superior turbinate. While there may still be debate about middle turbinate preservation in ESS, multiple studies have shown the lack of deleterious complication in judicious middle turbinate resection.\textsuperscript{23–25} Choby et al\textsuperscript{25} completed a systematic review of published literature to evaluate clinical outcomes of middle turbinate resection during ESS. Nine studies with a combined 2123 subjects were included in the final review, with two studies specifically focusing on olfaction outcomes.\textsuperscript{23,24} Both of the latter studies noted objective improvement in olfactory function postoperatively. This change may be associated with improved transport of odorants to the olfactory cleft following removal of obstructive middle turbinate tissue. However, the result from these studies should not serve as recommendation for indiscriminate middle turbinate resection in a bid to improve olfaction. The observations do provide healthy reassurance that when indicated, meticulous partial middle turbinate resection is relatively safe without fear of acute or long term complications. Partial middle turbinate resection should be performed judiciously when the surgeon believes this structure is contributing to disease burden, since continued presence increases the risk of postoperative complication and may serve as a primary obstacle to successful surgery. With respect to the superior turbinate, olfactory epithelium has been shown to be have a preferential anterior distribution. However, the limited data from small studies suggest that resection of the inferior third of the superior turbinate (during trans ethmoid sphenoidotomy) has no significant negative impact on olfaction.\textsuperscript{26,27}

The negative correlation between quantitative olfactory test scores and volumetric olfactory cleft opacification has been established.\textsuperscript{17,22} However, there is a paucity of prospective or randomized studies focused on olfactory ability after surgery targeting the olfactory cleft. Nguyen et al\textsuperscript{18} performed a single-surgeon prospective study in which olfactory function was evaluated by self-ratings on an analog scale and quantitative Sniffin’ Sticks test scores with a focus on patients requiring surgery in the olfactory cleft.
Neither the physical removal of diseased tissue from the olfactory cleft nor the histopathology were predictors of postoperative olfactory outcome. This may be counterintuitive since CRSwNP cohorts are expected to experience significant benefit from ESS via resolution of conductive loss. However, one could also posit that disease near the olfactory cleft may be associated with inflammatory changes which can cause irreversible sensorineural loss. In theory, patients requiring olfactory cleft surgery may have more severe disease and require a higher frequency of revision surgery, thereby being more likely to experience mechanical or cellular injury to olfactory epithelium.

**Conclusion**

CRS is associated with varying degrees of olfactory dysfunction, with the most dysfunction being evident in the prevalence of nasal polyps. ESS can provide clinically significant improvement in olfaction as measured via self-reports and quantitative testing. Benefit varies by CRS phenotype as patients demonstrating comorbid nasal polyps are more likely to demonstrate greater long term benefit from removal of lesions causing conductive loss. It is also possible that CRSwNP patients receive more aggressive postoperative medical therapy, including corticosteroids which reduce inflammation and thus alleviate sensorineural components of olfactory loss.

Surgery involving partial middle or superior turbinate resection may be performed judiciously without fear of postoperative iatrogenic anosmia, although more research in larger samples is clearly needed. There are limited studies evaluating long term outcomes of ESS in the olfactory cleft. Surgeons should generally proceed with caution and avoid mucosa stripping in this region unless specifically necessary to manage evident mucosal pathology.

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