Received: 21 July 2020 | Revised: 14 September 2020 | Accepted: 16 October 2020

DOI: 10.1002/lio2.485

REVIEW

Laryngoscope Investigative Otolaryngology

Olfaction: Sensitive indicator of inflammatory burden in chronic rhinosinusitis

Xiaoguang Yan MD[1] |
Katherine Lisa Whitcroft BSc MBChB (Hons) MRCS DOHNS[1,2] | Thomas Hummel MD[1]

[1]Smell and Taste Clinic, Department of Otorhinolaryngology, TU Dresden, Dresden, Germany

[2]UCL Ear Institute, University College London, London, UK

Correspondence
Thomas Hummel, MD, Smell and Taste Clinic, Department of Otorhinolaryngology, TU Dresden, Fetscherstrasse 74, Dresden 01307, Germany.
Email: thummel@msx.tu-dresden.de

Funding information
the Knut and Alice Wallenberg foundation

Abstract

Background and Objective: Olfactory dysfunction has a high prevalence in chronic rhinosinusitis (CRS) patients and significantly affects quality of life. CRS is recognized as a complex disorder encompassing heterogeneous inflammatory processes in the nose and paranasal sinuses. Olfactory dysfunction in CRS patients is associated with the level of inflammatory mediators and the efficiency of inflammatory control. Learning about the association between CRS-related inflammation and olfactory function will provide clues to the pathogenesis of CRS.

Structure: The first section of this review describes the assessment of olfactory function using various measures, from ratings to MR based imaging. Then, we discuss the conductive and inflammatory mechanisms related to olfactory dysfunction in CRS: olfaction is associated with certain inflammatory patterns and is potentially a marker of CRS subtype. Finally, we review anti-inflammatory therapies including conservative and surgical approaches, and their effectiveness in olfactory dysfunction in CRS.

Conclusion: Assessment of olfactory function should be considered in the clinical evaluation of CRS patients, not only for detecting and quantifying patients' symptom, but also because it appears to be useful to objectively assess the efficacy of CRS treatment over time. In addition, olfaction can be expected to expand the library of CRS phenotypes and endotypes and, hence, pave the way for more precise, tailored treatment options.

KEYWORDS

anosmia, chronic rhinosinusits, inflammation, nose, olfaction, smell

1 | INTRODUCTION

Olfaction, one of the basic human senses, has a wide range of functions, including the avoidance of environmental hazards, finding and identifying food,[1] spatial orientation,[2] flavor perception, social interactions (eg, recognition of emotions and romantic relationships),[3] and cognitive functions (eg, modulation of memories).[4] Patients with olfactory dysfunction are more likely to report difficulties with cooking, feeling less safe, and depression and anxiety. Unexplained olfactory dysfunction has also been related to increased mortality.[1,5] All in all, olfactory dysfunction can severely affect quality of life (QOL).

Olfactory dysfunction is among the cardinal diagnostic features (nasal blockage/obstruction/congestion, nasal discharge, facial pain/

pressure, and reduction or loss of smell) of chronic rhinosinusitis (CRS), which is defined as an inflammatory disease of the nasal cavities and paranasal sinuses lasting 12 weeks or longer.[6] Approximately 67% to -78% of CRS patients are affected by impaired olfaction,[7] and more and more researchers are focusing their attention on the sense of smell in CRS. (Figure 1) Olfactory dysfunction is deemed to be a major contributor to medication use and poor QOL in CRS patients.[8,9]

To date CRS is mainly clinically classified into the two main phenotypes: CRS without nasal polyps (CRSsNP) and with nasal polyps (CRSwNP). Over the past decade, research has begun to explore the heterogeneity of CRS by finding immuno-pathophysiologic mechanisms and defining inflammatory endotypes, In fact, the recent EPOS2020 position paper has divided CRS into: *Type 2* presenting with high level of Th2 cytokines, such as IL-4, IL-5, and IL-13, and infiltrating eosinophils, which is more resistant to therapies and exhibits a high rate of recurrence, while *nontype2* is related to Th1/Th17 immune responses characterized by cytokine IL-17A and IL-8 as well as excess neutrophilic inflammation and interferon-gamma (IFN-γ).[10] Biologic agents targeting type 2 inflammation hold great promise in providing targeted therapies in severe and recalcitrant CRS patients. At present, Dupilumab, a humanized monoclonal lgG4 antibody directed against the interleukin-4 receptor α (IL-4Rα) subunit, is the first biological to be approved by the Food and Drug Administration (FDA) of the USA and the European Medicines Agency (EMA) in 2019 for use in CRSwNP. Dupilumab shows significant improvement in almost all clinical symptoms of CRSwNP.[11] In light of such results, it has been suggested that biologicals as novel therapies in nonadequate disease control may potentially revolutionize CRSwNP treatment.[12]

Research efforts have been made to investigate the relation between endotype and phenotype of CRS. CRSwNP is known as a type 2 reaction, while CRSsNP is linked with predominantly Th-1 cell response.[13] Type 2 endotypes tend to be more resistant to current therapies and are associated with asthma.[14] Evidence also demonstrates olfactory dysfunction, a cardinal CRS symptom, to be strongly associated with the type 2 inflammatory endotype. Patients with eosinophilic CRS complain of a stronger degree of smell loss,[15] and the degree of smell function was found to be positively correlated with the inflammatory condition of the nasal cavity.[16] Given that the overall intensity of the inflammatory response is closely associated with the severity of disease and carries prognostic information, it seems important to understand the role of olfaction in CRS and its association with the inflammatory status.[17] In this paper, we aim to review olfactory dysfunction with regard to its clinical evaluation, pathophysiological mechanisms, relation with inflammatory burden and anti-inflammatory responses in CRS patients.

2 | ASSESSMENT OF OLFACTORY FUNCTION

2.1 | Subjective assessment

Subjective testing can be easily performed in daily clinical practice using visual analogue scales (VAS) and Likert-type questionnaires. Patients are asked to rate frequency and severity of their symptoms based on their experience of smell loss, which provides insights into the real-world impact of smell loss in CRS patients. It has been shown to be a simple, relatively reliable method to differentiate between normosmia and hyposmia/anosmia.[18,19] Therefore, "subjective" olfactory assessment appears to be helpful for olfaction screening when psychophysical tests are unavailable. Mattos et al showed that olfactory-specific questionnaires can be helpful for post-treatment follow-up, they also established the minimal clinically important difference of these questionnaires which helps to gauge clinically relevant differences in olfactory function, and the impact of interventions.[20] However, Philpott et al reported that only 28% patients in a rhinology clinic are aware of their olfactory function before being tested.[21] A survey at the clinic conducted by Lötsch et al have shown that almost 30% (355/1227) of anosmic subjects rated their ability to smell as at least "average".[22] On an individual level, much of the literature

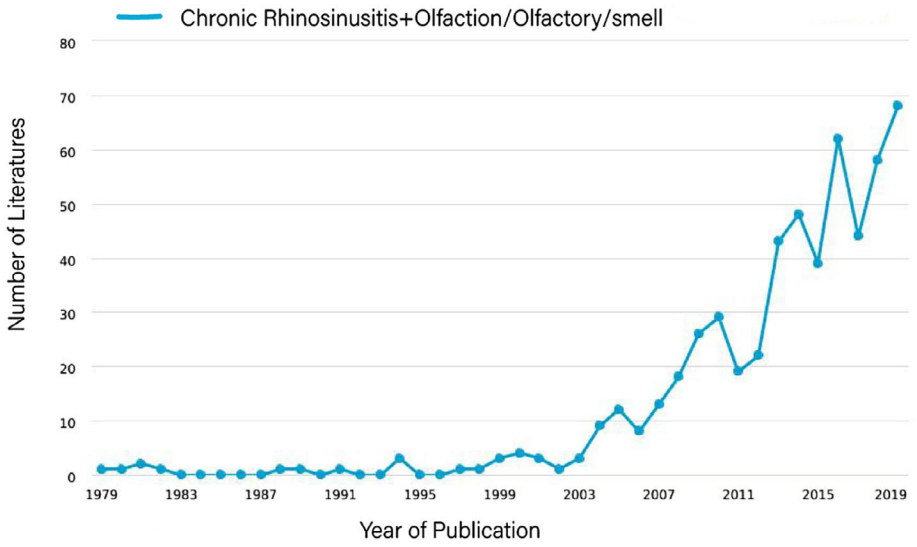

FIGURE 1 Number of literatures related to CRS and olfactory function published between the year 1979 and 2019. The key terms (["chronic rhinosinusitis"] and ["olfaction" or "olfactory" or "smell"]) were used to search relevant articles in Scopus (documents by year)

emphasized that there are striking differences between rated and measured olfactory function.[23,24]

Similarly, in a recent study of 109 patients with CRS, only a weak relationship between olfactory-specific QOL and psychophysical measures of olfactory function was found.[8] Interestingly, considering the nature of the sense of smell as determinant of flavor perception, it needs to be further investigated to what degree flavor loss is among the main drivers of CRS patients to seek medical counseling.[25,26] Indeed, increasing evidence shows low correlation between subjective symptoms and objective findings in CRS.[27] The gradual onset of smell loss in CRS may explain why olfactory loss often goes unnoticed.[28] Given this discrepancy, assessment of olfactory function based on self-reports is recommended to be performed in conjunction with psychophysical methods allowing for a more objective characterization of the sense of smell.[29]

2.2 | Psychophysical assessment of olfactory function

2.2.1 | Orthonasal tests

Orthonasal olfaction describes the perception of odors through sniffing. A number of standardized and validated orthonasal psychophysical olfactory tests have been developed. The "Sniffin' Sticks" test (Burghart; Wedel, Germany) and the Smell Identification Test (Sensonics Inc., Haddon Heights, New Jersey) are the two most widely used tests for clinical and research applications. While most tests focus on odor identification, the Sniffin Sticks, for example, is multicomponent and allows for the assessment of odor threshold, odor discrimination and identification. Combined testing of these components to diagnose smell loss appears to be more sensitive than individual tests, especially when including assessment of odor thresholds.[30] In CRS patients, odor threshold appears to be more affected than odor discrimination and identification, as shown in a study examining 1226 subjects.[31] This is in contrast to other disease etiologies: patients with postinfectious olfactory dysfunction, for example, have relatively well preserved odor threshold and discrimination during the period of recovery, but poor odor identification.[31] Multicomponent olfactory tests may therefore aid in diagnosing the underlying cause of impaired olfaction.

Whilst odor threshold may carry diagnostic information, in patients who have undergone treatment for CRS, it has been suggested that odor discrimination best reflects overall change in olfactory function.[32] In addition, odor discrimination has the strongest correlation with olfactory-specific QOL in CRS.[8]

In light of the above, validated and, if possible, multicomponent psychophysical olfactory tests can aid in diagnosis, quantitatively monitor patients' symptom and help to evaluate the efficiency of CRS therapy.[29]

2.2.2 | Retronasal tests

Many patients complain of taste loss. However, apart from a relatively small number of patients with gustatory dysfunction (sweet, sour, bitter, salty, and savory/umami), the symptom "taste loss" typically signals loss of flavor.[33] Retronasal olfaction, well described by Rozin[34] in 1982,is a critical element in flavor perception, related to smells that arise from inside the mouth during eating and drinking. Food-associated volatiles are carried by retronasal airflow reaching the olfactory epithelium upon exhalation rather than by orthonasal flow, due to the unique shape of the human oropharynx.[35] Studies based on magnetic resonance imaging (MRI) and electrophysiological recordings have demonstrated the processing of retronasal odors to be distinct from orthonasal perception of the same odors.[36,37]

Over the past two decades, methods for the clinical assessment of retronasal olfactory function have become available. Heilman et al[38] introduced a retronasal olfactory test using "taste powders" with grocery store condiments and food items (eg, spices and instant drinks). The taste powders are administered to the subject's oral cavity using squeezable plastic vials. Another retronasal olfactory test is "candy smell test" introduced by Renner et al,[39] comprised of 23 differently aromatized smell candies. Both tests are considered as easy to handle, reliable tools to investigate retronasal olfaction. Their results are well correlated with orthonasal function (eg, the "Sniffin' Sticks" scores) and differentiate normosmia, hyposmia, and anosmia. However, still some issues are present. Neither taste powders nor the "candies" are tasteless, other sensory modalities like the taste and/or texture may enhance the performance correctly during retronasal test. Powders are nonstandardized reagents, which may affect intertest results' reliability. Several new tools have been proposed. For example, "Candy Smell Test" for self-testing,[40] tasteless powders,[41] and freeze-dried retronasal stimuli.[42] What is more, currently, only retronasal odor identification is assessed which is strongly dependent on cultural backgrounds. Other possibilities to assess retronasal olfactory function may be expected in the future, for example, retronasal discrimination, or assessment of retronasal thresholds.

Retronasal and orthonasal odor identification are correlated in CRS patients.[43] Completely obstructing the olfactory cleft (OC) can significantly decrease orthonasal and retronasal olfactory function.[44] However, retronasal olfaction is more often preserved to a higher degree in CRSwP compared to orthonasal olfaction, supporting the idea that polyps mechanically change airflow to the OC.[45] A significant correlation was reported between retronasal olfaction and olfactory-specific QOL which was not found to the same degree for orthonasal function.[43] Retronasal olfaction can provide additional information when evaluating changes in eating habits. Moreover, regular exposure to retronasal odors ("retronasal training") may have the potential to improve food-related QOL.[46]

2.3 | Assessment of olfactory-related parameters using imaging and electrophysiological tools

CT and MRI allow the examination of olfaction-related structures. CT of the sinuses remains the modality of choice to confirm or exclude diagnosis and evaluate the severity of CRS. OC opacification quantified using CT has been shown to be an effective method to evaluate

olfactory function in patients with CRS.[47] It seems the association between OC opacification and olfactory function based on the nasal polyps. In 148 CRS patients, Catherine el al[48] found OC opacification only correlated with olfactory function in CRSwNP, whereas not in CRSsNP. Similarly, in Kohli's study, quantitative measures of OC opacification correlate with odor threshold, discrimination, and identification scores within the CRSwNP patients. However, in CRSsNP subgroup, odor thresholds correlate with OC opacification, while odor discrimination/identification do not.[49] In addition, whether retronasal olfactory function linked to CT opacification of the OC have been unclear in current literature. Apart from correlation with olfaction function, OC opacification may also help predict recovery of olfaction function after surgery in CRSwNP patients.[50]

Compared with CT, MRI offers unique advantages in the delineation of olfactory structures including olfactory bulbs, olfactory sulcus, olfactory tract, and olfactory cortex. For the olfactory bulb and sulcus, this works best in T2-weighted sequences due to the bright CSF surrounding these structures. Both olfactory bulb volume and olfactory sulcus depth have been shown to be of clinical relevance in various pathological conditions.[51-53] CRS patients exhibit a reduction in OB volume.[54,55] Importantly, a marked increase of OB volume was observed after treatment, concomitant with an increase in olfactory function.[56-58] In keeping with this, structural alterations in gray matter volume within olfactory-related regions has also been shown in CRS patients with olfactory impairments.[59] Moreover, grey matter volume within olfactory-eloquent regions increases after surgical treatment for CRS, along with improved olfactory function.[60] These dynamic changes in OB and gray matter volume reflect the apparent plastic nature of the olfactory system.

Therefore, CT/MRI-based volumetric analysis would appear to be a useful objective morphological tool to assess olfactory function in CRS patients, particularly in longitudinally tracking patients' recovery after treatment.

Other ways to evaluate olfactory function in a relatively unbiased way include olfactory event-related potentials (OERPs), functional magnetic resonance imaging (fMRI), or positron emission tomography (PET).[61-63] These methods allow deeper insights into the functional characterization of the human olfactory system, with the capability to explore the pathophysiology of smell dysfunction. However, these examinations are typically limited to use in research, partly due to their relatively high cost, and the need for specialized equipment and expertise.

3 | MECHANISMS FOR OLFACTORY LOSS IN CRS

The mechanisms underlying CRS-associated olfactory loss are not fully known. It has traditionally been assumed to be of a conductive origin, with the OC being mechanically obstructed by polyps/edematous mucosal tissue, leading to impaired airflow, and reduced odorant access to the olfactory epithelium. Recently, Besser et al effectively established a hyposmia model obstructed the OC with dissolvable nasal dressing.[44] In keeping with this, nasal polyps can affect orthonasal olfactory function more strongly than retronasal olfactory function, emphasizing conductive mechanisms in smell dysfunction.[64] While there is no doubt that nasal patency is essential for olfactory perception, observations in patients with CRS show that smell loss is possible even when the OC is nonobstructed and no changes in nasal airflow are present. Furthermore, removal of nasal polyps does not always increase olfactory function in CRS.[65,66] Hence, olfactory loss in CRS can also be attributed to inflammatory processes.

The histologic changes of olfactory mucosa in CRS patients include—goblet cell hyperplasia, squamous metaplasia, and more commonly, erosion, which is characterized by severe olfactory epithelial layers loss and a higher prevalence of inflammatory cell infiltration.[67-69] Inflammation within the olfactory epithelium may directly or indirectly decrease the quantity of olfactory neurons. Biopsies specimen of the olfactory epithelium in cases of olfactory dysfunction secondary to CRS showed apoptotic changes.[67] In the mouse, progressive inflammatory infiltration in the olfactory epithelium triggers caspase-3 activity, known as the executioner caspase in apoptosis, leading to olfactory neuron death in CRS.[70,71] Eosinophilic inflammation directly impairs or even kills olfactory sensory neurons, resulting possibly from neurotoxic effects from the release of eosinophilic granule proteins and eosinophil-related cytokine damage.[72-74] Compared with the noneosinophilic CRS group, eosinophilic CRS patients have a more pronounced smell loss, fewer OMP (olfactory marker protein: a protein that marks mature olfactory neurons used in immunohistochemistry) positive cells and greater epithelial erosion.[75] Recent work in mice suggests that type 2 inflammation decreases the number of immature olfactory neurons, but not the mature olfactory neurons, indicating that it may interfere with the process of olfactory neurogenesis.[76] After some time, this may lead to reduced mature olfactory neuron populations, resulting in reduced OMP+ cells, as mentioned above.

Inflammation can also have a negative impact on the overlying mucus layer of the respiratory and olfactory epithelium. Mucus is secreted by respiratory submucosal glands (SMGs) and Bowman's glands.[77] Inflammation may lead to hypersecretion, in turn leading to altered potassium and sodium concentrations within the olfactory mucus. Accordingly, disruption of the ionic milieu may interfere with olfactory receptor activation and downstream transduction cascades.[78,79] Furthermore, there is evidence from animal models of CRS showing that olfactory stem cell proliferation and differentiation are arrested with local inducible expression of TNF-a and interferon-c.[80-83] Importantly, olfactory receptor neurons can reverse these changes when such inflammation subsides.[81,84]

It is believed that the immune system plays a major role in CRS development. Emerging evidence suggests olfactory stem cell to be involved in crosstalk between CRS inflammatory microenvironment and immune cells, which switch from their regenerative state to immune defense, resulting in impaired neurogenesis and olfactory neuron replacement.[85] This work has expanded the underlying mechanisms of CRS-related smell loss and the possibility of developing novel therapies.

As mentioned above, changes in the central olfactory system are associated with smell loss in CRS. Reduced olfactory bulb volume has been demonstrated in CRS patients with smell loss.[55,56] In rodents, recent studies suggest that persistent nasal inflammation induces glial activation, damage of the olfactory bulb circuit, and ultimately atrophy of the olfactory bulb.[86] Of particular interest, change in olfactory bulb volume is related to change in odor threshold, which is considered to partly reflect peripheral olfactory function. Given that olfactory bulb directly receives axons from the olfactory receptor neurons, the decrease of olfactory bulb volume in CRS might be due to decreasing input from the olfactory epithelium. In addition, structural and integrity changes in white matter and gray matter related to the olfactory areas have also been demonstrated.[59,87,88] It indicates that an inflammatory state in the nasal cavity is sufficient to produce a gradual and accumulated effect in central areas, which may contribute to the smell loss in CRS patients. It remains unknown which specific processes are responsible for these changes in central-nervous structures, what these changes mean for prognosis and how they could be utilized in the clinical treatment of CRS related olfactory loss. It appears that smell loss in CRS is one of the best example for central changes due to peripheral inflammation and obstruction- and that timely therapy (and associated diagnosis) of CRS is crucial.

Hence, impaired olfactory function in CRS patients is multifactorial. It not only results from physical obstruction of the nasal cavity, but also involves an inflammatory component resulting in olfactory receptor neuron dysfunction and death. What is more, CRS appears to affect the entire olfactory system, from the *periphery to central-nervous areas*. Although many recent advances remain in preclinical stages, knowledge of CRS-associated olfactory loss contributes to the development of future therapeutic approaches.

4 | OLFACTION INDICATES THE DEGREE OF INFLAMMATION AND MAY BE A MARKER OF CRS SUBTYPE

Previous histological studies of olfactory tissue in CRS demonstrated that CRS patients with olfactory deficit exhibited a higher degree of inflammation with an influx of lymphocytes, macrophages, and eosinophils.[67] An increasing number of studies support the idea that olfactory function is quantitatively associated with the level of inflammatory mediators. In a cross-sectional analysis of 34 patients with olfactory loss due to CRS, Schlosser et al found that scores of olfactory function were inversely correlated with levels of IL-5 in the OC.[89] Furthermore, one prospective case-control study showed that odor identification scores in CRS patients related to the degree of IL-2, IL-5, IL-6, IL-10, and IL-13 collected from olfactory mucus.[90] Of note, a direct correlation was found between the cytokine levels in the OC and levels in the middle meatus,[90] which suggests that cytokine changes are found simultaneously in the respiratory mucosa and the olfactory mucosa. These results are consistent with the previous observation of a significant correlation between the eosinophil counts in the respiratory and olfactory mucosa.[67,75]

Olfactory loss seems to be more severe and occurs at earlier stages of the disease in patients with eosinophilic infiltration.[9] The smell reduction of CRS has been reported to show correlations with blood and nasal mucosa eosinophil count.[91,92] The eosinophilic marker, Charcot-Leyden crystal (CLC) gene expression, has been found to be significantly correlated with olfactory threshold, even when confounders that is, the presence of nasal polyps, radiographic and endoscopic findings, were controlled.[93] In addition, in both the CRSsNP and CRSwNP groups, olfactory test scores have been shown to be negatively correlated with neuron-specific enolase (NSE) levels.[16] Given this evidence, it appears that the severity of olfactory function serves as a surrogate marker of inflammation within the entire nasal cavity, not just the local environment in the area of the OC.

Multicomponent psychophysical olfactory testing (ie, assessment of odor threshold, discrimination, identification) increases sensitivity in diagnosing olfactory dysfunction. In a study involving 1226 hyposmic patients, Whitcroft et al found patients with CRS related smell loss to have particularly impaired odor threshold (ie, they had a low sensitivity), relative to odor identification and discrimination.[31] This study suggested that the pattern of subtest scores provides diagnostic benefit regarding the underlying pathology. In line with this evidence, Lavin et al showed that threshold scores are associated with eosinophilia, as measured by CLC, more closely than discrimination score.[93] In contrast, data from Schlosser et al, in a much smaller group, indicate that olfactory identification rather than threshold correlates best with OC mucus IL-5,[89] which is one of the essential cytokines that activate type 2 helper T-cell (Th2) inflammation. Considering the limited number of studies, the present interpretation is that different patterns of smell test scores may be associated with different CRS endotypes, with the Th2 predominant inflammatory profile producing injury to the olfactory epithelium. More studies are needed to clarify this.

The evolving classification of CRS helps to successfully tailor patient care. The division of CRS into two major phenotypes, CRSsNP and CRSwNP, is widely accepted. Smell loss has been described as a major feature of CRSwNP affecting 83% to 91% of patients. What is more, olfactory function is more severe and more frequent as reported by patients with CRSwNP compared to CRSsNP patients.[7,94] Recently, there has been effort to identify phenotypic subgroups by using clustering methods, based on common clinical symptoms. In these studies, olfactory function seems to be a stable and valuable factor in the various clusters. In a multi-institutional prospective study of 690 patients in CRS, separating patients into five clusters, olfactory function at baseline was significantly different between clusters. Moreover, patient clusters with the best olfactory function experience the greatest benefit with surgery.[95] Cole et al identified five clusters depending on the severity and frequency of symptoms using 37 questions from 3535 subjects. The results indicated that self-reported smell loss is a factor with little longitudinal change.[96] In Morse et al's study, the majority of anosmic patients were found in a specific CRS cluster characterized by nasal polyposis (100%), allergic fungal rhinosinusitis (50%), and aspirin-exacerbated respiratory disease (AERD) (33%).[97] These results suggest that olfactory function is a

cardinal symptom that can be used to identify sub-phenotypes of CRS, which may provide prognostic information. Subclassification of CRS is underway for better understanding of CRS endotypes. Studies point out that smell loss may also be closely related to Th2-skewed inflammatory CRS endotype.[97]

Taken together, these results provide important insights into olfactory function in CRS which is linked to the sinonasal inflammatory response: it appears to be an indicator of CRS severity. Accurate, quantitative assessment of smell function, with well-established and reliable tools, should continue to aid in the establishment of CRS phenotypes and endotypes, as well as the optimization of available treatments.

4.1 | Therapies of olfactory function in CRS

The plasticity of the olfactory system allows recovery after treatment of CRS related olfactory dysfunction.[98] The first-line therapy of olfactory function in CRS is to treat the underlying sinonasal condition.[29] Accordingly, olfactory function has been shown to respond to both medical and surgical interventions in CRS (Table 1).

4.1.1 | Conservative approaches

Standard conservative treatment of CRS is based on glucocorticosteroids, administered orally, for example, prednisolone, or topically via nasal spray/drops, for example, fluticasone, mometasone, or beclametasone. Both administration forms have been shown to be effective in improving olfactory function in CRS patients: A meta-analysis showed that orally administered glucocorticosteroids improve both self-rated and psychophysically assessed function, compared to placebo, included studies used prednisolone (30-50 mg/day) for 14 days and 32 mg methylprednisolone tapered off over 20 days compared to placebo.[99,100] However, oral steroids seem to improve olfaction only for a short period of time (8-12 weeks).[101] Topical steroids have also been shown to be effective in terms of subjectively rated olfactory function. However, as discussed above, subjective and objective testing have been shown to correlate poorly—with subjective ratings being confounded by numerous factors including nasal airflow and the patients expectations.[27] Yousefi et al's study revealed there are not significantly improvement in olfactory threshold among 16 CRSsNP patients after 3 months topical corticosteroids and nasal irrigation of normal saline (P = .311 for men and P = .139 for women).[102]

The therapeutic efficacy of topical steroids seems to depend strongly on the mode of application.[103] Steroid nasal drops administered in the supine position with the head tilted back in patients with CRS and nasal polyps (CRSwNP) was prospectively shown to improve olfactory threshold and identification scores on the Conneticut Chemosensory Clinical Research Center (CCCRC) test.[104] In addition, work by Shu and colleagues showed that the application of nasal spray more directly to the OC using a longer applicator provides

TABLE 1 Anti-inflammatory approaches regarding olfactory function outcome to CRS patients (heterogeneous approaches in terms of methods used and groups of patients studied)

Reference	Anti-inflammatory approach (conservative, surgical, biologicals)	EG/ controls (n)	Patients phenotype	Follow-up	Measure of olfaction	Outcome (significance)
Vaidyanathan et al[100]	Oral corticosteroids	29/29	CRSwNP	2 wk	VAS for smell (scale 0-100)	Predicted mean difference = −28.3 (P = .002)
Yousefi et al[102]	topical corticosteroids and nasal irrigation of normal saline	16/17	CRSsNP	1, 3 mo	smell threshold test	Mean difference = .33 (P = .31 for men, P = .14 for women)
Dadgarnia et al[110]	ESS	40	CRSwNP	3 mo	Smell identification test (range 0-24)	Mean difference = 2.3 (P = .001)
Paksoy et al[111]	Surgical and standardized medical treatment	30	CRSwNP	3 mo	Sniffin' Sticks (range 1-48)	Mean difference = 6.8 (P < .001)
Wong et al[112]	Draf III surgery Frontal Sinus Surgery	104	recalcitrant CRS	30.6 mo	Likert scale for smell (range 0-5)	Significant improvement (71% vs 28%, P < .01)
Bachert et al[11]	Dupilumab	438/286	CRSwNP	24 wk	UPSIT (range 0-40)	Predicted mean difference = 11.3 (P < .0001)

Abbreviations: CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyposis; CRSwNP, chronic rhinosinusitis with nasal polyposis; EG, experimental group; ESS, endoscopic sinus surgery; UPSIT, The University of Pennsylvania Smell Identification Test; VAS, visual analogue scale.

significantly better results in terms of olfactory outcome compared to conventional nasal sprays.[105]

Separate from anti-inflammatory effects, evidence from animal work shows that glucocorticoids can upregulate cyclic nucleotide-gated (CNG) channels, so potentially enhancing olfactory receptor response (olfactory receptors are G-protein coupled receptors that involve the activation of CNG during their transduction cascades). In addition, glucocorticoids can increase the production of intracellular cAMP within olfactory receptor neurons, again enhancing transduction cascades.[106] Finally, glucocorticoids can induce the apoptosis of mature olfactory receptor neurons, and cytokines released after apoptosis can support the regeneration of olfactory receptor neurons.[107]

When systemic steroids are considered, there is no widely accepted agreement regarding the dose, frequency and duration of use. Notably, there is little research where patients have been followed up for a year or longer, there is still a lack of knowledge about the long-term efficacy of steroids in the treatment of smell loss secondary to CRS. Furthermore, the association of osteonecrosis with the use of systemic steroids cannot be ignored by doctors and patients.[108]

Currently existing evidence does not provide support for improvement of olfactory function with antibacterial and antifungal treatment.[99]

4.1.2 | Surgical approaches

Endoscopic sinus surgery (ESS) for patients with CRS is the most common and important therapy for medically refractive patients.[6] The goal of ESS for CRS is to clear polyps and excess polypoid tissue, optimize sinus function, and facilitate use of topical treatments, all of which help improve the inflammatory response and might restore olfactory function. CRS associated olfactory function has been shown to benefit from ESS.[94,109-111] Significant olfactory improvement was also observed in recalcitrant CRS by Draf III sinus surgery.[112] Revision ESS has been shown to restore odor identification abilities in nearly half of patients studied.[113] However, some patients experience no improvement or even deterioration in olfactory function after surgery. For example, Jiang et al showed that surgery seems to have no improvement on olfactory function for patients with medically refractory symptoms.[114] One large prospective study (n = 775) using standardized odor identification tests demonstrated that only 23% of CRS patients received olfactory improvement, 68% no improvement, and 9% deterioration after ESS.[115] In contrast, in a 5 year follow-up study in 34 patients, 9% of CRS patients had no improvement and 6% had deterioration after ESS, based on measures of odor thresholds.[116] Therefore, olfactory outcomes after ESS are variable, and it remains challenging to predict surgical outcome in individuals.

ESS for CRS can also help to improve overall QoL, and smell improvement is positively associated with patients' QoL changes. An increase in olfactory function of 4.75 points on the composite threshold + discrimination + identification Sniffin' Sticks score is considered the cutoff point for clinically significant QoL recovery.[117] Notably, olfactory dysfunction before ESS has been described as a helpful predictor for postoperative QoL outcomes.[118] Thus, olfactory assessment is an important preoperative step for case selection and counseling regarding expected surgical outcomes.

Many studies have attempted to find reliable predictors of olfactory outcome after ESS. Nasal polyposis seems to play a key role in olfactory function in CRS patients.[94,115,119] Previous work has shown only 13.5% of CRSwNP patients to be normosmic, and about half of such patients to be anosmic, in this study, ESS significantly improved severely impaired olfactory function in CRSwNP patients at 6 months after treatment.[120] Polyposis of the OC is crucial and should receive special attention.[121] Of note, co-existent pathology in CRSwNP, for example, respiratory epithelial adenomatoid hamartomas (REAH), a benign tumor, present in 48% of biopsied oedematous OCs in the study by Lorentz et al, should be included in the differential diagnosis of nasal polyposis.[122] Nasal polyposis is significantly associated with better outcomes in postoperative olfactory function.[94] Other research has indicated the following predictors for a positive surgical outcome: anosmia, no prior surgery, opacification of the OC, and favorable wound healing status.[123-127] Furthermore, olfactory changes after administration of systemic glucocorticosteroid therapy predicts the olfactory outcome after sinus surgery in CRSwNP.[128]

ESS with steroid nasal spray has been compared to steroid nasal spray alone in a recent prospective study. In both groups olfactory function improved after treatment. However, remission rate was greater in the ESS group (60%) compared to the conservative group (20%).[129] In a prospective, multi-center study, CRS patients treated with ESS had better olfactory function than who were treated with medication.[130] in contrast, some studies revealed that there were no significant differences in olfactory function between ESS and standard medical therapy groups.[102,131] These differences in outcome may be due in part to the heterogeneity in patients involved and to methods used for assessment. Further studies involving larger samples of participants and more sensitive, unified measures of olfaction are required.

Finally, olfactory deterioration has been considered the most sensitive indicator for CRS recurrence.[132,133]

4.1.3 | Use of biologicals

If surgical and medical treatment fails, biologicals can be considered for a growing number of CRS patients. Dupilumab, a humanized monoclonal IgG4 antibody directed against the interleukin-4 receptor α (IL-4Rα) subunit, is the first targeted biologic therapy for the treatment of CRSwNP, which was approved in the European Union and the USA in 2019. Significant loss of smell has become one of six criteria needed to use biologicals.[6] Placebo-controlled clinical studies have demonstrated efficacy of dupilumab in improving clinical aspects of CRS, based on endoscopy, radiography and measures of QOL. The sense of smell improved from baseline rapidly (within the first 4 weeks) and significantly (by more than 10 points after 24 weeks, using the 40-item Smell Identification Test).[11] Omalizumab, another antibody targeting IgE, has also be shown to improve olfactory

awareness scores in comparison to a control group.[134] Cavaliere reported a case study of a patient with olfactory dysfunction secondary to CRSwNP, the patient experienced complete recovery from anosmia with the anti-IL-5 monoclonal antibody mepolizumab treatment.[135] The range of antibodies targeted in the treatment of CRS can be expected to continue to expand. Furthermore, biological treatments may be combined with surgery or glucocorticosteroids in future care pathways.

As discussed above, olfactory function in CRS is significantly associated with the sinonasal inflammatory response, as well as response to anti-inflammatory treatments: e.g. application of glucocorticosteroids directly to the OC, polyp removal from the OC, or biological treatment. Olfaction can therefore be used as a marker for inflammatory state and to predict response to treatment.

5 | CONCLUSION

Olfactory dysfunction, with a high prevalence in CRS patients, has a significant impact on health and QOL. Detailed assessment of olfactory function should be considered in the clinical evaluation of CRS patients, especially with well-established and reliable psychophysical testing, not only for detecting and quantifying patients' symptom, but also because it is useful to objectively assess the efficacy of CRS treatment over time. In particular, olfactory function seems to be a stable and valid factor in the various clusters of clinical presentations, linked with certain inflammatory patterns and reflective of the response to anti-inflammatory treatment. Accordingly, olfaction may act as a marker in the progression of chronic sinonasal inflammation, help to differentiate CRS phenotypes and endotypes and ultimately aid in the development of tailored treatment regimens.

ACKNOWLEDGMENT

TH and YXG are funded by the Knut och Alice Wallenbergs Stiftelse. Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

Xiaoguang Yan, Katherine Lisa Whitcroft, and Thomas Hummel declare that they have no conflict of interest.

ORCID

Katherine Lisa Whitcroft https://orcid.org/0000-0002-1417-0049
Thomas Hummel https://orcid.org/0000-0001-9713-0183

REFERENCES

1. Croy I, Nordin S, Hummel T. Olfactory disorders and quality of life—an updated review. *Chem Senses*. 2014;39:185-194.
2. Dahmani L, Patel RM, Yang Y, Chakravarty MM, Fellows LK, Bohbot VD. An intrinsic association between olfactory identification and spatial memory in humans. *Nat Commun*. 2018;9:4162.
3. Hofer MK, Collins HK, Whillans AV, Chen FS. Olfactory cues from romantic partners and strangers influence women's responses to stress. *J Pers Soc Psychol*. 2018;114:1-9.
4. Doty RL. Olfactory dysfunction in neurodegenerative diseases: is there a common pathological substrate? *Lancet Neurol*. 2017;16:478-488.
5. Pinto JM, Wroblewski KE, Kern DW, Schumm LP, McClintock MK. Olfactory dysfunction predicts 5-year mortality in older adults. *PLoS ONE*. 2014;9:e107541.
6. Fokkens WJ, Lund VJ, Hopkins C, et al. European position paper on Rhinosinusitis and nasal polyps 2020. *Rhinology*. 2020;58:1-464.
7. Kohli P, Naik AN, Harruff EE, Nguyen SA, Schlosser RJ, Soler ZM. The prevalence of olfactory dysfunction in chronic rhinosinusitis. *Laryngoscope*. 2017;127:309-320.
8. Mattos JL, Schlosser RJ, Storck KA, Soler ZM. Understanding the relationship between olfactory-specific quality of life, objective olfactory loss, and patient factors in chronic rhinosinusitis. *International Forum of Allergy & Rhinology*. 2017;7:734-740.
9. Katotomichelakis M, Simopoulos E, Zhang N, et al. Olfactory dysfunction and asthma as risk factors for poor quality of life in upper airway diseases. *Am J Rhinol and Allergy*. 2013;27:293-298.
10. Wang X, Zhang N, Bo M, et al. Diversity of T cytokine profiles in patients with chronic rhinosinusitis: a multicenter study in Europe, Asia, and Oceania. *J Allergy Clin Immunol*. 2016;138:1344-1353.
11. Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet*. 2019;394:1638-1650.
12. Stevens WW, Peters AT, Tan BK, et al. Associations between inflammatory Endotypes and clinical presentations in chronic Rhinosinusitis. *J Allergy Clin Immunol Practice*. 2019;7:2812-2820.
13. Tomassen P, Vandeplas G, Van Zele T, et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. *J Allergy Clin Immunol*. 2016;137:1449-1456.
14. Turner JH, Li P, Chandra RK. Mucus T helper 2 biomarkers predict chronic rhinosinusitis disease severity and prior surgical intervention. *Int Forum Allerg Rhinol*. 2018;8:1175-1183.
15. Thompson CF, Price CPE, Huang JH, et al. A pilot study of symptom profiles from a polyp vs an eosinophilic-based classification of chronic rhinosinusitis. *Int Forum Allerg Rhinol*. 2016;6:500-507.
16. Tsybikov NN, Egorova EV, Kuznik BI, Fefelova EV, Magen E. Neuron-specific enolase in nasal secretions as a novel biomarker of olfactory dysfunction in chronic rhinosinusitis. *Am J Rhinol Allergy*. 2016;30:65-69.
17. Jiang N, Kern RC, Altman KW. Histopathological evaluation of chronic rhinosinusitis: a critical review. *Am J Rhinol Allergy*. 2013;27:396-402.
18. Frasnelli J, Hummel T. Olfactory dysfunction and daily life. *Eur Arch Otorhinolaryngol*. 2005;262:231-235.
19. Zou L-Q, Linden L, Cuevas M, et al. Self-reported mini olfactory questionnaire (self-MOQ): a simple and useful measurement for the screening of olfactory dysfunction. *The Laryngoscope*. 2019. https://doi.org/10.1002/lary.28419.
20. Mattos JL, Schlosser RJ, Mace JC, Smith TL, Soler ZM. Establishing the minimal clinically important difference for the questionnaire of olfactory disorders. *Int Forum Allergy Rhinol*. 2018;8:1041-1046.
21. Philpott CM, Rimal D, Tassone P, Prinsley PR, Premachandra DJ. A study of olfactory testing in patients with rhinological pathology in the ENT clinic. *Rhinology*. 2008;46:34-39.
22. Lötsch J, Hummel T. Clinical usefulness of self-rated olfactory performance-a data science-based assessment of 6000 patients. *Chem Senses*. 2019;44:357-364.
23. Welge-Luessen A, Hummel T, Stojan T, Wolfensberger M. What is the correlation between ratings and measures of olfactory function in patients with olfactory loss? *Am J Rhinol*. 2005;19:567-571.
24. Haxel BR, Bertz-Duffy S, Fruth K, Letzel S, Mann WJ, Muttray A. Comparison of subjective olfaction ratings in patients with and without olfactory disorders. *J Laryngol Otol*. 2012;126:692-697.
25. Spence C. Multisensory flavor perception. *Cell*. 2015;161:24-35.
26. Oleszkiewicz A, Park D, Resler K, et al. Quality of life in patients with olfactory loss is better predicted by flavor identification

than by Orthonasal olfactory function. *Chem Senses*. 2019;44:371-377.
27. Landis BN, Hummel T, Hugentobler M, Giger R, Lacroix JS. Ratings of overall olfactory function. *Chem Senses*. 2003;28:691-694.
28. Gaines AD. Anosmia and hyposmia. *Allergy Asthma Proc*. 2010;31:185-189.
29. Hummel T, Whitcroft KL, Andrews P, et al. Position paper on olfactory dysfunction. *Rhinology*. 2016;56:1-30.
30. Lötsch J, Reichmann H, Hummel T. Different odor tests contribute differently to the evaluation of olfactory loss. *Chem Senses*. 2007;33:17-21.
31. Whitcroft KL, Cuevas M, Haehner A, Hummel T. Patterns of olfactory impairment reflect underlying disease etiology. *Laryngoscope*. 2017;127:291-295.
32. Whitcroft KL, Cuevas M, Andrews P, Hummel T. Monitoring olfactory function in chronic rhinosinusitis and the effect of disease duration on outcome. *Int Forum Allergy Rhinol*. 2018;8:769-776.
33. Deems DA, Doty RL, Settle RG, et al. Smell and taste disorders, a study of 750 patients from the University of Pennsylvania Smell and taste center. *Arch Otolaryngol—Head & Neck Surg*. 1991;117:519-528.
34. Rozin P. "Taste-smell confusions" and the duality of the olfactory sense. *Percept Psychophys*. 1982;31:397-401.
35. Ni R, Michalski MH, Brown E, et al. Optimal directional volatile transport in retronasal olfaction. *Proc Natl Acad Sci USA*. 2015;112:14700-14704.
36. Heilmann S, Hummel T. A new method for comparing orthonasal and retronasal olfaction. *Behav Neurosci*. 2004;118:412-419.
37. Small DM, Gerber JC, Mak YE, Hummel T. Differential neural responses evoked by orthonasal versus retronasal odorant perception in humans. *Neuron*. 2005;47:593-605.
38. Heilmann S, Strehle G, Rosenheim K, Damm M, Hummel T. Clinical assessment of retronasal olfactory function. *Arch Otolaryngol—Head & Neck Surg*. 2002;128:414-418.
39. Renner B, Mueller CA, Dreier J, Faulhaber S, Rascher W, Kobal G. The candy smell test: a new test for retronasal olfactory performance. *Laryngoscope*. 2009;119:487-495.
40. Besser G, Tianxiang Liu D, Prem B, et al. Retronasal olfactory testing using candies sent by post and for screening purposes: a feasibility study. *Rhinology*. 2020;58:218-225.
41. Yoshino A, Goektas G, Mahmut MK, et al. A new method for assessment of Retronasal olfactory function. *Laryngoscope*. 2020. https://doi.org/10.1002/lary.28698.
42. Pal P, Shepherd D, Hamid N, Hautus MJ. The use of freeze-dried retronasal stimuli to assess olfactory function. *Clin Otolaryngol*. 2019;44:770-777.
43. Othieno F, Schlosser RJ, Storck KA, Rowan NR, Smith TL, Soler ZM. Retronasal olfaction in chronic rhinosinusitis. *Laryngoscope*. 2018;128:2437-2442.
44. Besser G, Liu DT, Renner B, Hummel T, Mueller CA. Reversible obstruction of the olfactory cleft: impact on olfactory perception and nasal patency. *Int Forum Allergy & Rhinol*. 2020;10:713-718.
45. Ganjaei KG, Soler ZM, Storck KA, Rowan NR, Othieno FA, Schlosser RJ. Variability in Retronasal odor identification among patients with chronic Rhinosinusitis. *Am J Rhinol and Allergy*. 2018;32:424-431.
46. Besser G, Oswald MM, Liu DT, Renner B, Mueller CA. Flavor education and training in olfactory dysfunction: a pilot study. *Eur Arch Otorhinolaryngol*. 2020;277:1987-1994.
47. Soler ZM, Pallanch JF, Sansoni ER, et al. Volumetric computed tomography analysis of the olfactory cleft in patients with chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2015;5:846-854.
48. Loftus C, Schlosser RJ, Smith TL, et al. Olfactory cleft and sinus opacification differentially impact olfaction in chronic rhinosinusitis. *Laryngoscope*. 2020;130:2311-2318.
49. Kohli P, Schlosser RJ, Storck K, Soler ZM. Olfactory cleft computed tomography analysis and olfaction in chronic rhinosinusitis. *Am J Rhinol Allergy*. 2016;30:402-406.
50. Vandenhende-Szymanski C, Hochet B, Chevalier D, Mortuaire G. Olfactory cleft opacity and ct score are predictive factors of smell recovery after surgery in nasal polyposis. *Rhinology*. 2015;53:29-34.
51. Hummel T, Urbig A, Huart C, Duprez T, Rombaux P. Volume of olfactory bulb and depth of olfactory sulcus in 378 consecutive patients with olfactory loss. *J Neurol*. 2015;262:1046-1051.
52. Negoias S, Croy I, Gerber J, et al. Reduced olfactory bulb volume and olfactory sensitivity in patients with acute major depression. *Neuroscience*. 2010;169:415-421.
53. Rombaux P, Potier H, Markessis E, Duprez T, Hummel T. Olfactory bulb volume and depth of olfactory sulcus in patients with idiopathic olfactory loss. *Eur Arch Otorhinolaryngol*. 2010;267:1551-1556.
54. Herzallah IR, Askar SM, Amer HS, Ahmed AF, El-Anwar MW, Eesa MH. Olfactory bulb volume changes in patients with sinonasal polyposis: a magnetic resonance imaging study. *Otolaryngol Head Neck Surg*. 2013;148:689-693.
55. Rombaux P, Potier H, Bertrand B, Duprez T, Hummel T. Olfactory bulb volume in patients with sinonasal disease. *Am J Rhinol*. 2008;22:598-601.
56. Alarabawy RA, Eltomey MA, Shehata EM. Volumetric study of the olfactory bulb in patients with chronic rhinonasal sinusitis using MRI. *Egypt J Radiol Nucl Med*. 2016;47:487-491.
57. Gudziol V, Buschhüter D, Abolmaali N, Gerber J, Rombaux P, Hummel T. Increasing olfactory bulb volume due to treatment of chronic rhinosinusitis—A longitudinal study. *Brain: A Journal of Neurology*. 2009;132:3096-3101.
58. Shehata EM, Tomoum MO, Amer MA, Alarabawy RA, Eltomey MA. Olfactory bulb neuroplasticity: a prospective cohort study in patients with chronic rhinosinusitis with nasal polyps. *Clin Otolaryngol*. 2018;43:1528-1534.
59. Han P, Whitcroft KL, Fischer J, et al. Olfactory brain gray matter volume reduction in patients with chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2017;7:551-556.
60. Whitcroft KL, Fischer J, Han P, et al. Structural plasticity of the primary and secondary olfactory cortices: increased gray matter volume following surgical treatment for chronic Rhinosinusitis. *Neuroscience*. 2018;395:22-34.
61. Han P, Zang Y, Hummel C, Faria V, Hummel T. Short or long runs: an exploratory study of odor-induced fMRI design. *The Laryngoscope*. 2020;130:1110-1115.
62. Zatorre RJ, Jones-Gotman M, Evans AC, Meyer E. Functional localization and lateralization of human olfactory cortex. *Nature*. 1992;360:339-340.
63. Lascano AM, Hummel T, Lacroix JS, Landis BN, Michel CM. Spatio-temporal dynamics of olfactory processing in the human brain: an event-related source imaging study. *Neuroscience*. 2010;167:700-708.
64. Landis BN, Giger R, Ricchetti A, et al. Retronasal olfactory function in nasal polyposis. *Laryngoscope*. 2003;113:1993-1997.
65. Hox V, Bobic S, Callebaux I, Jorissen M, Hellings PW. Nasal obstruction and smell impairment in nasal polyp disease: correlation between objective and subjective parameters. *Rhinology*. 2010;48:426-432.
66. Doty RL, Mishra A. Olfaction and its alteration by nasal obstruction, rhinitis and rhinosinusitis. *Laryngoscope*. 2001;111:409-423.
67. Kern RC. Chronic sinusitis and anosmia: pathologic changes in the olfactory mucosa. *Laryngoscope*. 2000;110:1071-1077.
68. Yee KK, Pribitkin EA, Cowart BJ, et al. Neuropathology of the olfactory mucosa in chronic rhinosinusitis. *Am J Rhinol Allergy*. 2010;24:110-120.

69. Yee KK, Pribitkin EA, Cowart BJ, Rosen D, Feng P, Rawson NE. Analysis of the olfactory mucosa in chronic rhinosinusitis. *Ann N Y Acad Sci*. 2009;1170:590-595.
70. Kern RC, Conley DB, Haines GK 3rd, Robinson AM. Pathology of the olfactory mucosa: implications for the treatment of olfactory dysfunction. *Laryngoscope*. 2004;114:279-285.
71. Ge Y, Tsukatani T, Nishimura T, Furukawa M, Miwa T. Cell death of olfactory receptor neurons in a rat with nasosinusitis infected artificially with staphylococcus. *Chem Senses*. 2002;27:521-527.
72. Acharya KR, Ackerman SJ. Eosinophil granule proteins: form and function. *J Biol Chem*. 2014;289:17406-17415.
73. Li L, Walker TL, Zhang Y, Mackay EW, Bartlett PF. Endogenous interferon gamma directly regulates neural precursors in the non-inflammatory brain. *J Neurosci*. 2010;30:9038-9050.
74. Epstein VA, Bryce PJ, Conley DB, Kern RC, Robinson AM. Intranasal Aspergillus fumigatus exposure induces eosinophilic inflammation and olfactory sensory neuron cell death in mice. *Otolaryngol Head Neck Surg*. 2008;138:334-339.
75. Kashiwagi T, Tsunemi Y, Akutsu M, Nakajima I, Haruna S. Postoperative evaluation of olfactory dysfunction in eosinophilic chronic rhinosinusitis–comparison of histopathological and clinical findings. *Acta Oto-Laryngol*. 2019;139:881-888.
76. Rouyar A, Classe M, Gorski R, et al. Type 2/Th2-driven inflammation impairs olfactory sensory neurogenesis in mouse chronic rhinosinusitis model. *Allergy*. 2019;74:549-559.
77. Rubin JS. Smell and taste in health and disease. *Int J Pediatric Otorhinolaryngol*. 1992;24:195-196.
78. Kern RC, Foster JD, Pitovski DZ. Glucocorticoid (type II) receptors in the olfactory mucosa of the Guinea-pig: RU 28362. *Chem Senses*. 1997;22:313-319.
79. Selvaraj S, Liu K, Robinson AM, et al. In vivo determination of mouse olfactory mucus cation concentrations in normal and inflammatory states. *PLoS ONE*. 2012;7:e39600.
80. Turner JH, Liang KL, May L, Lane AP. Tumor necrosis factor alpha inhibits olfactory regeneration in a transgenic model of chronic rhinosinusitis-associated olfactory loss. *Am J Rhinol Allergy*. 2010;24:336-340.
81. Lane AP, Turner J, May L, Reed R. A genetic model of chronic rhinosinusitis-associated olfactory inflammation reveals reversible functional impairment and dramatic neuroepithelial reorganization. *J Neurosci*. 2010;30:2324-2329.
82. Pozharskaya T, Lane AP. Interferon gamma causes olfactory dysfunction without concomitant neuroepithelial damage. *Int Forum Allergy Rhinol*. 2013;3:861-865.
83. Sousa Garcia D, Chen M, Smith AK, Lazarini PR, Lane AP. Role of the type I tumor necrosis factor receptor in inflammation-associated olfactory dysfunction. *Int Forum Allergy Rhinol*. 2017;7:160-168.
84. Turner JH, May L, Reed RR, Lane AP. Reversible loss of neuronal marker protein expression in a transgenic mouse model for sinusitis-associated olfactory dysfunction. *Am J Rhinol Allergy*. 2010;24:192-196.
85. Chen M, Reed RR, Lane AP. Chronic inflammation directs an olfactory stem cell functional switch from Neuroregeneration to immune defense. *Cell Stem Cell*. 2019;25:501-513.
86. Hasegawa-Ishii S, Shimada A, Imamura F. Neuroplastic changes in the olfactory bulb associated with nasal inflammation in mice. *J Allergy Clin Immunol*. 2019;143:978-989.e973.
87. Güllmar D, Seeliger T, Gudziol H, et al. Improvement of olfactory function after sinus surgery correlates with white matter properties measured by diffusion tensor imaging. *Neuroscience*. 2017;360:190-196.
88. Taha T, Megahed AA, Taha MS, Mahmoud H, Rabie TM, Askora AM. Diffusion tensor imaging: a smart move to olfactory pathway imaging; comparative study of chronic sinonasal polyposis patients and normal control. *Egypt J Radiol Nucl Med*. 2020;51:34.
89. Schlosser RJ, Mulligan JK, Hyer JM, Karnezis TT, Gudis DA, Soler ZM. Mucous cytokine levels in chronic Rhinosinusitis-associated olfactory loss. *JAMA Otolaryngol Head Neck Surg*. 2016;142:731-737.
90. Wu J, Chandra RK, Li P, Hull BP, Turner JH. Olfactory and middle meatal cytokine levels correlate with olfactory function in chronic rhinosinusitis. *Laryngoscope*. 2018;128:E304-E310.
91. Soler ZM, Sauer DA, Mace J, Smith TL. Relationship between clinical measures and histopathologic findings in chronic rhinosinusitis. *Otolaryngol Head Neck Surg*. 2009;141:454-461.
92. Wu D, Li Y, Bleier BS, Wei Y. Superior turbinate eosinophilia predicts olfactory decline in patients with chronic rhinosinusitis. *Annals Allergy Asthma Immunol*. 2020;125:304-310.
93. Lavin J, Min JY, Lidder AK, et al. Superior turbinate eosinophilia correlates with olfactory deficit in chronic rhinosinusitis patients. *Laryngoscope*. 2017;127:2210-2218.
94. Litvack JR, Mace J, Smith TL. Does olfactory function improve after endoscopic sinus surgery? *Otolaryngol Head Neck Surg*. 2009;140:312-319.
95. Soler ZM, Hyer JM, Rudmik L, Ramakrishnan V, Smith TL, Schlosser RJ. Cluster analysis and prediction of treatment outcomes for chronic rhinosinusitis. *J Allergy Clin Immunol*. 2016;137:1054-1062.
96. Cole M, Bandeen-Roche K, Hirsch AG, et al. Longitudinal evaluation of clustering of chronic sinonasal and related symptoms using exploratory factor analysis. *Allergy*. 2018;73:1715-1723.
97. Morse JC, Shilts MH, Ely KA, et al. Patterns of olfactory dysfunction in chronic rhinosinusitis identified by hierarchical cluster analysis and machine learning algorithms. *Int Forum Allergy Rhinol*. 2019;9:255-264.
98. Konkimalla A, Tata PR. Plasticity in olfactory epithelium: is it a sniffer or shape shifter? *Cell Stem Cell*. 2017;21:707-708.
99. Banglawala SM, Oyer SL, Lohia S, Psaltis AJ, Soler ZM, Schlosser RJ. Olfactory outcomes in chronic rhinosinusitis with nasal polyposis after medical treatments: a systematic review and meta-analysis. *Int Forum Allergy Rhinol*. 2014;4:986-994.
100. Vaidyanathan S, Barnes M, Williamson P, Hopkinson P, Donnan PT, Lipworth B. Treatment of chronic rhinosinusitis with nasal polyposis with oral steroids followed by topical steroids: a randomized trial. *Ann Intern Med*. 2011;154:293-302.
101. Poetker DM, Jakubowski LA, Lal D, Hwang PH, Wright ED, Smith TL. Oral corticosteroids in the management of adult chronic rhinosinusitis with and without nasal polyps: an evidence-based review with recommendations. *Int Forum of Allergy & Rhinology*. 2013;3:104-120.
102. Yousefi J, Madarshahi H, Akhavan A, et al. Effect of ESS on olfactory threshold of patients with CRS without nasal polyps. *Int Tinnitus J*. 2018;22:89-92.
103. Mori E, Merkonidis C, Cuevas M, Gudziol V, Matsuwaki Y, Hummel T. The administration of nasal drops in the "Kaiteki" position allows for delivery of the drug to the olfactory cleft: a pilot study in healthy subjects. *Eur Arch Otorhinolaryngol*. 2016;273:939-943.
104. Mott AE, Cain WS, Lafreniere D, Leonard G, Gent JF, Frank ME. Topical corticosteroid treatment of anosmia associated with nasal and sinus disease. *Arch Otolaryngol—Head & Neck Surg*. 1997;123:367-372.
105. Shu C-H, Lee P-L, Shiao A-S, Chen K-T, Lan M-Y. Topical corticosteroids applied with a squirt system are more effective than a nasal spray for steroid-dependent olfactory impairment. *Laryngoscope*. 2012;122:747-750.
106. Ohta Y, Takanosawa M, Matumoto C, Makino N, Ishimoto S, Ichimura K. High-dose glucocorticoids inhibit proliferation of rat olfactory epithelium. *Ann Otol Rhinol Laryngol*. 2002;111:909-911.

107. Simpson PJ, Miller I, Moon C, Hanlon AL, Liebl DJ, Ronnett GV. Atrial natriuretic peptide type C induces a cell-cycle switch from proliferation to differentiation in brain-derived neurotrophic factor- or nerve growth factor-primed olfactory receptor neurons. *J Neurosci*. 2002;22:5536-5551.
108. Dilisio MF. Osteonecrosis following short-term, low-dose oral corticosteroids: a population-based study of 24 million patients. *Orthopedics*. 2014;37:e631-e636.
109. Saedi B, Sadeghi M, Yazdani N, Afshari A. Effectiveness of FESS in smell improvement of sinusitis patients. *Indian J Otolaryngol Head Neck Surg*. 2013;65:283-287.
110. Dadgarnia M, Rahmani A, Baradaranfar M, et al. The relationship between endoscopic and radiologic findings and olfactory status of patients with chronic rhinosinusitis with nasal polyps before and after the endoscopic sinus surgery. *Eur Arch Otorhinolaryngol*. 2019;276:397-400.
111. Paksoy ZB, Cayonu M, Yucel C, Turhan T. The treatment efficacy of nasal polyposis on olfactory functions, clinical scoring systems and inflammation markers. *Eur Arch Otorhinolaryngol*. 2019;276:3367-3372.
112. Wong EH, Do TQ, Harvey RJ, Orgain CA, Sacks R, Kalish L. Patient-reported olfaction improves following outside-in Draf III frontal sinus surgery for chronic rhinosinusitis. *Laryngoscope*. 2019;129:25-30.
113. Hsu CY, Wang YP, Shen PH, Weitzel EK, Lai JT, Wormald PJ. Objective olfactory outcomes after revision endoscopic sinus surgery. *Am J Rhinol Allergy*. 2013;27:e96-e100.
114. Jiang R-S, Lu F-J, Liang K-L, et al. Olfactory function in patients with chronic rhinosinusitis before and after functional endoscopic sinus surgery. *Am J Rhinol*. 2008;22:445-448.
115. Pade J, Hummel T. Olfactory function following nasal surgery. *Laryngoscope*. 2008;118:1260-1264.
116. Briner HR, Jones N, Simmen D. Olfaction after endoscopic sinus surgery: long-term results. *Rhinology*. 2012;50:178-184.
117. Katotomichelakis M, Simopoulos E, Tripsianis G, et al. Improvement of olfactory function for quality of life recovery. *Laryngoscope*. 2013;123:E10-E16.
118. Katotomichelakis M, Simopoulos E, Tripsianis G, et al. Predictors of quality of life outcomes in chronic rhinosinusitis after sinus surgery. *Eur Arch Otorhinolaryngol*. 2014;271:733-741.
119. Schriever VA, Gupta N, Pade J, Szewczynska M, Hummel T. Olfactory function following nasal surgery: a 1-year follow-up. *Eur Arch Otorhinolaryngol*. 2013;270:107-111.
120. Federspil PA, Wilhelm-Schwenk R, Constantinidis J. Kinetics of olfactory function following endonasal sinus surgery for nasal polyposis. *Rhinology*. 2008;46:184-187.
121. Kuperan AB, Lieberman SM, Jourdy DN, Al-Bar MH, Goldstein BJ, Casiano RR. The effect of endoscopic olfactory cleft polyp removal on olfaction. *Am J Rhinol Allergy*. 2015;29:309-313.
122. Lorentz C, Marie B, Vignaud JM, Jankowski R. Respiratory epithelial adenomatoid hamartomas of the olfactory clefts. *Eur Arch Otorhinolaryngol*. 2012;269:847-852.
123. Oka H, Tsuzuki K, Takebayashi H, Kojima Y, Daimon T, Sakagami M. Olfactory changes after endoscopic sinus surgery in patients with chronic rhinosinusitis. *Auris Nasus Larynx*. 2013;40:452-457.
124. Minwegen F, Thomas JP, Bernal-Sprekelsen M, Dazert S, Minovi A. Predictive value of disease severity on self-reported rating and quantitative measures of olfactory function outcomes after primary endoscopic sinus surgery. A prospective study. *Rhinology*. 2014;52:437-443.
125. Mohanty S. Effect of endoscopic sinus surgery on olfaction: a prospective analysis. *Clin Rhinol*. 2016;9:115-119.
126. Szaleniec J, Wrobel A, Strek P, et al. Smell impairment in chronic rhinosinusitis—evaluation of endoscopic sinus surgery results and review of literature concerning olfactory function predictors. *Otolaryngol Pol*. 2015;69:33-44.
127. Kim DW, Kim JY, Kim SW, Jeon SY. Postoperative olfactory results in chronic rhinosinusitis with nasal polyposis according to wound healing status. *Clin Exper Otorhinolaryn*. 2013;6:146-151.
128. Bogdanov V, Walliczek-Dworschak U, Whitcroft KL, Landis BN, Hummel T. Response to Glucocorticosteroids predicts olfactory outcome after ESS in chronic rhinosinusitis. *Laryngoscope*. 2020;130:1616-1621.
129. Baradaranfar MH, Ahmadi ZS, Dadgarnia MH, et al. Comparison of the effect of endoscopic sinus surgery versus medical therapy on olfaction in nasal polyposis. *Eur Arch Otorhinolaryngol*. 2014;271:311-316.
130. Deconde AS, Mace JC, Alt JA, Schlosser RJ, Smith TL, Soler ZM. Comparative effectiveness of medical and surgical therapy on olfaction in chronic rhinosinusitis: a prospective, multi-institutional study. *Int Forum Allergy Rhinol*. 2014;4:725-733.
131. Savvateeva DM, Kochetkov PA, Lopatin AS. The influence of the surgical and medicamental treatment on the olfactory function in the patients presenting with polypous rhinosinusitis. *Vestn Otorinolaringol*. 2012;2:31-35.
132. Kovář D, Holý R, Voldřich Z, Fundová P, Astl J. The contribution of CT navigation in endoscopic sinus surgery: an evaluation of patient postoperative quality of life and olfaction function results. *Otorinolaryngol Foniatr*. 2017;66:205-209.
133. Simmen DB, Jones NS. Olfaction and nasal polyposis. In: Önerci TM, Ferguson BJ, eds. *Nasal Polyposis: Pathogenesis, Medical and Surgical Treatment*. Berlin, Heidelberg: Springer Berlin Heidelberg; 2010:163-173.
134. Gevaert P, Calus L, Van Zele T, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. *J Allergy Clin Immunol*. 2013;131:110-116.
135. Cavaliere C, Incorvaia C, Frati F, et al. Recovery of smell sense loss by mepolizumab in a patient allergic to dermatophagoides and affected by chronic rhinosinusitis with nasal polyps. *Clin Mol Allergy*. 2019;17:3-3.

How to cite this article: Yan X, Whitcroft KL, Hummel T. Olfaction: Sensitive indicator of inflammatory burden in chronic rhinosinusitis. *Laryngoscope Investigative Otolaryngology*. 2020;5:992–1002. https://doi.org/10.1002/lio2.485