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REVIEW

Olfactory Dysfunction in Chronic Rhinosinusitis

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Abstract

Purpose of review Chronic rhinosinusitis (CRS) is a prevalent and heterogeneous inflammatory disease that affects millions of people worldwide. Olfactory dysfunction (OD) is one of the most common symptoms of CRS patients. Increasing evidence suggests that the mechanisms underlying OD in different clinical subtypes and inflammatory endotypes of CRS may show discrepancy. Additionally, assessing the severity of OD in CRS patients, and selecting appropriate and effective treatment approaches have emerged as critical concerns in clinical practice. This article aims to provide new insights into the pathogenesis, diagnosis and treatment of OD in patients with CRS.

Recent findings Recent studies have further highlighted the heterogeneity of CRS, categorizing it into Type 2 and non-Type 2 subtypes based on distinct inflammatory patterns. Furthermore, the diverse mechanisms of OD in patients with different subtypes of CRS have been revealed. Beyond the conventionally recognized conductive factors, inflammatory factors are increasingly being identified as crucial pathogenic contributors to OD in patients with CRS. Generally, the evaluation methods for OD mainly include three different categories, including self-reported assessments based on questionnaires or scales, psychophysical tests, and electrophysiological or imaging assessments. Despite considerable efforts on new approaches, the long-term and effective treatments of OD in CRS still remain elusive. Olfactory training (OT) can be recommended for patients with OD, although it requires further evaluation in CRS patients.

Summary This article, based on recent progress, overviewed the epidemiological characteristics and pathophysiological mechanisms of OD in CRS patients, and summarized the methods of clinical assessment and treatment strategies of OD. We emphasized the diverse mechanisms of OD in different subtypes of CRS. Although drugs, biological products, and OT may be beneficial for improving olfactory function in CRS patients, further research is needed to confirm their long-term efficacy and develop more effective treatment approaches for OD in CRS.

Keywords Chronic rhinosinusitis · Olfactory dysfunction · Mechanisms · Type 2 inflammation · Treatment

Introduction

Chronic rhinosinusitis (CRS) is one of the most common chronic inflammatory diseases worldwide [1••, 2]. CRS is a heterogeneous disorder that affects approximately 12% of individuals in the United States, and 11% in Europe [3–6]. In China the prevalence is about 8% [7].The clinical symptoms of CRS include nasal congestion, rhinorrhea and headache. Besides, olfactory dysfunction (OD) is one of the most common symptoms [1••, 3, 8••], which seriously affects the quality of patients' life (QOL) and consumes a large number of medical resources [9].

Increasing evidence suggests that the OD of CRS patients may be caused by various mechanisms, which may be related to conductive factors and inflammatory factors [8••]. With the deepening understanding of the intrinsic type of

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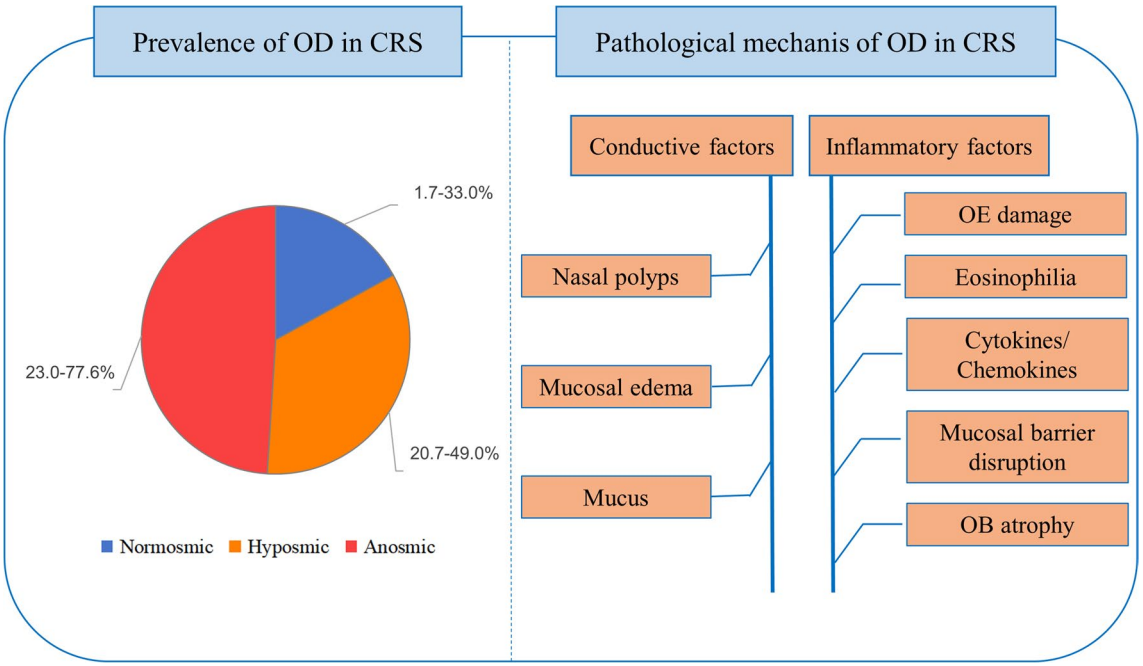

Fig. 1 The prevalence and pathological mechanisms of OD in CRS. OE, olfactory epithelium; OD, olfactory dysfunction; CRS, chronic rhinosinusitis; OB, olfactory bulb

inflammation and associated biomarkers, the heterogeneity of CRS has been thoroughly recognized. The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 have redefined the classification of CRS [1••], categorizing it into type 2 and non-type 2. Increasing studies have found that the mechanisms of OD in different subtypes of CRS may be distinct [1••]. In addition, the assessment of OD in CRS patients has become challenge in clinical practice, as well as the selection of appropriate and effective treatment methods. This article aims to review the research progress on the epidemiology, pathogenesis, assessment methods, and treatment strategies of OD in CRS patients.

Epidemiology

OD is a common clinical manifestation of CRS patients, which may also be one of the initial symptoms [1••, 3, 10•]. The severity of OD is closely related to the severity of disease [11]. Most studies indicate that approximately 60% to 80% of CRS patients experience varying degrees of OD [3, 12, 13]. However, several studies reported different data. A study from Japan found that only 38% of CRS patients suffer from OD [14]. Although the incidence of OD in CRS may be influenced by different olfactory assessments, the differences in OD prevalence among different geographical regions and ethnic backgrounds are still unclear (Fig. 1). More studies are needed to reveal the geographical and ethnic differences in the incidence of OD in CRS. OD significantly affects QOL [15–17], and both CRS and OD have been shown to be associated with depression, severely affecting the mental health of patients [18, 19]. In CRS, OD is independently correlated with the risks factors such as smoking, nasal polyps, and aspirin-exacerbated respiratory disease (AERD), as well as diabetes and age [13, 20, 21] (Table 1). Traditionally, the diagnosis of CRS is based on sinus CT and endoscopic examination to determine the presence of nasal polyps, and it is divided into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) [3, 22]. Compared to CRSsNP patients, CRSwNP patients have a higher incidence of OD and more severe symptoms [12, 21, 23] (Table 1). In addition, according to the latest classification, a study of 811 CRS patients found that the incidence of OD in type 2 and non-type 2 CRSwNP was 86.1% and 71.0%, respectively [24]. However, for most CRSsNP patients, although subjective OD was reported, only 17% of patients exhibited OD determined through objective measurements [13].

Pathophysiological Mechanisms of OD in CRS Patients

The Olfactory System

The olfactory system is primarily composed of the olfactory epithelium (OE) and the central olfactory bulb (OB) (Fig. 2). OE is the surface layer of the olfactory mucosa (OM), which captures odor molecules through the ciliary olfactory

receptors of olfactory sensory neurons (OSNs), thereby activating olfactory signals [25]. The main cellular components of the OE include OSNs, basal cells (globose basal cells and horizontal basal cells, GBCs & HBCs), olfactory sustentacular cells (OSCs), and Bowman gland cells, olfactory ensheathing cells (OECs) [26]. OSNs are the main sensory cells within the olfactory system. Mature OSNs have axons that pass through the cribriform plate to connect with the OB, as well as dendrites that infiltrate the epithelial surface to capture odor molecules in the nasal cavity through cilia [27]. Basal cells, especially HBCs, are responsible for differentiating into new OSNs or other type of cells to maintain cell renewal and regeneration in the olfactory system [28]. OSCs provide nutritional, metabolic, and other support for OSNs and the entire OE, and maintain the function of OSNs by endocytosing odor binding proteins/odor complexes [25, 29]. Bowman gland cells secrete mucus to keep the nasal cavity moist, providing a suitable microenvironment for OSNs, which promoting the generation and transmission of olfactory signals [22], and OECs ensheath, accompany and guide the axons of OSNs, and providing them with support, protection, and immune defense [30]. In addition, OB is the terminal nucleus of the olfactory nerve and the main central nervous system site for olfaction [31], after OSNs transmit olfactory information to OB, OB processes and integrates it and projects to the main olfactory centers, such as the limbic system (emotion) and hypothalamus (memory), and ultimately reaching the olfactory cortex, enabling people to acquire olfactory awareness [10•].

Pathological Mechanisms

The traditional view is that the OD of CRS patients is mainly attributed to the conductive factors (conductive OD) [32]. The olfactory cleft (OC) is the region where OE is located. Pathological changes in the nasal cavity of CRS patients, including mucosal edema and the formation of nasal polyps [3], may obstruct the OC and restrict the transmission of odorants to the OE, thereby affecting olfactory function [32] (Fig. 1). Hence, the presence of nasal polyps has a significant impact on OD (Table 2). Nasal polyps in the olfactory region may disperse olfactory airflow and olfaction [33]. Therefore, polyps can substantially reduce olfactory function when they are located in the olfactory region or when their size leads to significant obstruction of the nasal cavity [33]. However, if the small polyps are only located in the middle meatus, its impact on olfactory function is relatively mild [33].

In addition to conductive factors, an increasing number of studies indicate that inflammatory factors (sensorineural OD) are important for the development of OD in CRS patients [13] (Fig. 1). OD is closely related to histopathological changes of OE in CRS patients [34]. Inflammation may cause damage of OE (Fig. 2). Inflammation may lead to morphological changes and a decrease in the number of OSNs, ultimately result in OD in CRS patients [31, 35]. Under inflammation, axonal degeneration, dendrite loss, ciliary damage, and apoptosis of OSNs are frequently observed [18, 36]. In addition, the inflammation, by damaging other cells within the olfactory system that are responsible for supporting, repairing, and protecting OSNs, can disrupt olfactory function [18, 31, 37]. For instance, recent study found that the number of undifferentiated HBCs significantly increased in OE due to chronic inflammation [37]. Chronic inflammation is able to direct an olfactory stem cell function switch from neuro regeneration to immune defense [37]. Another study also found that the number of immature OSNs in the OM of type 2 inflammatory mice decreased, while the number of mature sensory neurons was not affected. This may be due to the reduction of OSNs renewal, which may be related to the regenerative function of OSNs [38, 39]. Moreover, inflammation can directly damage OSCs. A significant impact is the disruption of nutrition and metabolism in OSNs, as well as impairments in the generation and transmission of olfactory signals [26, 37]. Inflammation can also lead to the impairment of Bowman gland cells and OECs. Damage to these cells impairs the moistening and self-cleaning functions of the nasal cavity and sinuses, compromising the integrity of the mucosal barrier. In turn, the destruction of the mucosal barrier affects the protective immune function of OSNs [22, 30, 40]. In addition, under the long-term impact of chronic inflammation, abnormal proliferation and differentiation of olfactory epithelial cells occur during tissue injury and repair (Fig. 2). This condition manifests as squamous metaplasia and substitution of the olfactory epithelium by respiratory epithelium [41]. The respiratory epithelium is characterized by goblet cell hyperplasia, which is often interspersed with OSCs within the OE [41, 42]. These changes may disrupt the normal structure and function of OE, potentially affecting olfactory function [38, 41, 42]. In addition, besides Bowman gland cells, goblet cells in the OE may also affect olfaction by alter the volume and composition of mucus in OC[18]. Excessive mucus may block the nasal cavity and olfactory channels, preventing odor molecules from reaching the olfactory receptors [43]. Changes in the chemical composition of mucus may also affect the local microenvironment, interfering with the binding of odor molecules to olfactory receptors on the cilia of OSNs [43, 44]. Additionally, impairment of olfactory mucosal barrier usually occurs in chronic inflammation induced CRS, especially in type 2 inflammatory response [38, 45, 46]. The breakdown of the barrier makes it easier for foreign and intrinsic antigens (pathogenic microorganisms, toxins, and inflammatory products, etc.) to enter the olfactory nerve pathway, further exacerbating OD

Table 1 Summary of the references on the epidemiology of OD in CRS

Reference	Patients	Diagnostic method CRS	Olfaction measures	Prevalence OD%(NO.)	Outcome/results
Alobid et al. (2011) [11]	245CRSwNP	EPOS 2007	BAST-24	NR	Asthma, especially persistent asthma, had an accumulative impact on the loss of smell in patients with NP
Soler et al. (2016) [15]	51CRSwNP 70CRSsNP	AAO-HNS	SIT- 40	N:28% (34), H:49% (59), A:23% (28)	Asthma, allergy, AERD, obstructive sleep apnea, NP, and steroid dependency were associated with OD
Mattos et al. (2017) [16]	65CRSwNP 44 CRSsNP	EPOS 2012	Sniffin' Sticks QOD-NS	NR	QOD-NS correlated with non-white race, depression, SNOT-22 score, and TDI score in patients with CRS
Litvack et al. (2009) [20]	137CRSwNP 230CRSsNP	AAO-HNS	SIT-40	N:28% (122), H:49% (166), A:23% (79)	Patients with OD were more likely to have NP, asthma, acetylsalicylic acid intolerance, and/or a history of prior sinus surgery
Schlosser et al. (2020) [21]	224CRS	AAO-HNS	Sniffin' Sticks	N:27% (60), H:40% (90), A:33% (74)	OD was driven by polyps, asthma, diabetes, and age
Macchi et al. (2023) [24]	1)656CRSwNP (Type 2 group) 2)155CRSwNP (non-type 2 group)	EPOS 2020	Sniffin' Sticks	N:13.9% (91), OD:86.1% (565) N:29.0% (45), OD:71.0% (110)	Type 2 CRSwNP patients had a higher incidence of OD compared with non-Type 2 CRSwNP patients
Wu et al. (2018) [52]	36CRSwNP 31CRSsNP	EPOS 2012	SIT-40	NR	The levels of inflammatory mediators in OC mucus were associated with olfactory identification scores in CRS patients
Soler et al. (2020) [49]	37CRSwNP 25CRSsNP	AAO-HNS	Sniffin' Sticks	NR	The CRSwNP group had significantly worse olfactory function compared with the CRSsNP group
Schlosser et al. (2016) [48]	15CRSwNP 19CRSsNP	AAO-HNS	Sniffin' Sticks	NR	The TDI scores were lower in patients with CRSwNP than in patients with CRSsNP
Morse et al. (2019) [57]	61CRSwNP 49CRSsNP	EPOS 2012	SIT-40	NR	Asthma status, polyp status, AERD, CT score, tissue eosinophilia, and prior surgery were variables that predict olfactory function
Mori et al. (2013) [58]	418CRS	AAO-HNS	T&T olfactometry, intravenous olfactory test	NR	OC polyps, ethmoid opacification in CT, asthma, current smoking and age ≥ 50 years were associated with OD in CRS
Lavin et al. (2017) [63]	36CRSwNP 37CRSsNP	NR	Sniffin' Sticks, UPSIT	NR	Markers of eosinophils were elevated in the superior turbinate of patients with CRSwNP and correlated with loss of smell

Table 1 (continued)

Reference	Patients	Diagnostic method CRS	Olfaction measures	Prevalence OD%(NO.)	Outcome/results
Hauser et al. (2017) [39]	32CRSwNP 27CRSsNP	EPOS 2012	SIT-40	NR	Tissue eosinophilia was associated with loss of smell in CRSwNP
Kanemitsu et al. (2020) [65]	38CRSwNP 18CRSsNP	NR	Open Essence method	NR	OD was correlated with sputum eosinophil counts in CRS patients
Lee et al. (2023) [79]	724CRS	NR	patient-reported loss of smell score UPSIT	N:5% (36) OD:95% (688)	Opacification of the ethmoid, sphenoid and frontal sinuses in CT was associated with severe smell loss
Loftus et al. (2019) [80]	75CRSwNP 73CRSsNP	AAO-HNS	Sniffin' Sticks QOD-NS	NR	The opacification of the OC in CT was associated with OD
Haxel et al. (2022) [85]	1)72CRSwNP (Preoperative group) 2)47CRSwNP (operative group)	NR	Sniffin' Sticks	1) N:33% (24), H:42% (30), A:25% (18) 2) N:30% (14), H:43% (20), A:28% (13)	The degree of recovery of olfaction after ESS seemed to be most relevant in patients with high polyp scores
Mattos et al. (2021) [87]	61CRSwNP 52CRSsNP	NR	Sniffin' Sticks, QOD-NS, OCES	N:23% (26), H:43% (49), A:34% (38)	NP and previous ESS decreased the odds of postoperative improvement of OD, while septoplasty increased these odds
Mullol et al. (2022) [93]	724CRSwNP	NR	patient-reported loss of smell score, UPSIT	N:1.7% (12), H:20.7% (147), A:77.6% (551)	Low HRQoL assessed by SNOT-22, asthma, NSAID-ERD, and prior sinonasal surgery were associated with OD

A = anosmic; AAO-HNS = American Academy of Otolaryngology and Head and Neck Surgery; AERD = aspirin-exacerbated respiratory disease; BAST-24 = Barcelona Smell Test 24; CRS = chronic rhinosinusitis; CRSsNP = chronic rhinosinusitis without polyps; CRSwNP = chronic rhinosinusitis with nasal polyposis; CT = computed tomography; EPOS = European Position Paper on Sinusitis; ESS = endoscopic sinus surgery; H = hyposmic; HRQoL = health-related quality of life; N = normosmic; NP = nasal polyps; NR = not reported; NSAID-ERD = non-steroidal anti-inflammatory drug-exacerbated respiratory disease; OC = olfactory cleft; OCES = Olfactory Cleft Endoscopy Scale; OD = olfactory dysfunction; QOD-NS = Questionnaire of Olfactory Disorders–Negative Statements; SIT-40 = 40-item Smell Identification Test; SNOT-22 = 22-item Sinonasal Outcome Test; T&T = Toyota & Takagi; UPSIT = the University of Pennsylvania Smell Identification Test; TDI= Threshold, Discrimination, Identification

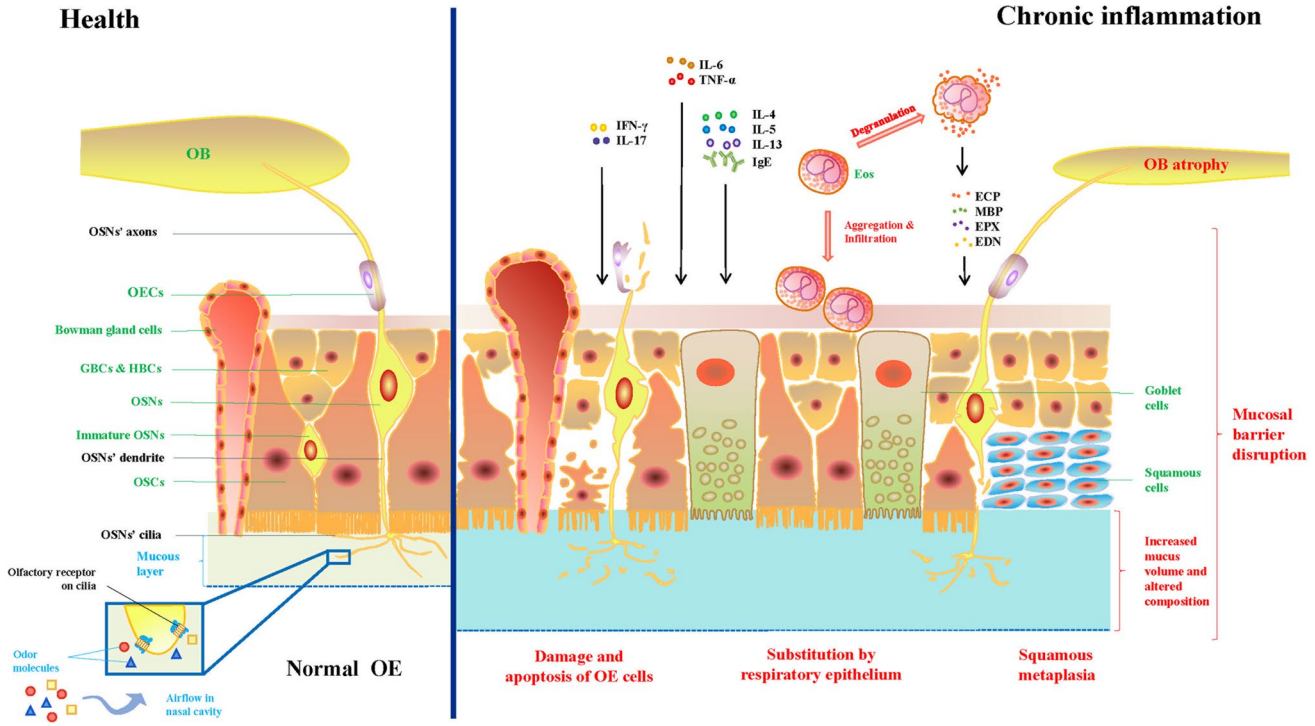

Fig. 2 The illustration of the structure of the olfactory system and the inflammation induced damage leading to OD in CRS patients, including damage and apoptosis of OE cells, substitution of the olfactory epithelium by respiratory epithelium, squamous metaplasia, aggregation and infiltration of eosinophils, mucosal barrier disruption, OB atrophy. OE, olfactory epithelium; OB, olfactory bulb; OSNs, olfactory sensory neurons; OECs, olfactory ensheathing cells; GBCs, globose basal cells; HBCs, horizontal basal cells; OSCs, olfactory sustentacular cells; Eos, eosinophils; IFN-γ, interferon-gamma; IL, interleukin; TNF-α, tumor necrosis factor-alpha; IgE, immunoglobulin E; ECP, eosinophil cationic protein; MBP, major basic protein; EPX, eosinophil peroxidase; EDN, eosinophil-derived neurotoxins

[18, 45, 47]. Many inflammatory cytokines have been found to be associate with OD in CRS patients (Fig. 2).

Pre-inflammatory cytokines such as interleukin(IL)-6 and tumor necrosis factor-alpha(TNF-α), and inflammatory cytokines including IL-2, IL-4, IL-5, IL-10, IL-13, interferon-gamma(IFN-γ), IL-17, as well as chemokines including C–C motif chemokine ligand(CCL)2、CCL5、CCL11, which are related to OD[1••, 2, 18, 48–53] (Table 2). Most of these cytokines and chemokines have potential neurotoxicity [54, 55], which may lead to damage and apoptosis of OSNs and cause temporary or permanent OD. However, a recent clustering analysis study based on the mucosal biomarkers collected from the OC of CRS patients showed that clusters dominated by type 2 inflammatory cytokines IL-5, IL-13, and immunoglobulin E(IgE) exhibited relatively low olfactory scores [56]. This result is consistent with another study clustering CRS cytokines, which also revealed a strong correlation between IL-5, IL-13 levels and olfactory function [57]. These data indicate that type 2 cytokines are more likely to lead to OD in CRS [38]. Additionally, TNF-α is a pleiotropic cytokine that has been universally associated with CRS [2], which inhibits the regeneration of OE by inhibiting the proliferation of basal progenitor cells and the production of immature OSNs [50]. The infiltration of eosinophils in the OM is one of the most common pathological changes in CRS [21, 58]. Compared with non-type 2 CRS and CRSsNP, both type 2 CRS and CRSwNP exhibit more significant eosinophil aggregation [38]. The aggregation of eosinophils is associated with the severity of inflammation in CRS and closely related to the OD [59]. A study on pathological examination and immunohistochemical analysis of OM in CRS patients found that OD patients had more severe erosion of the OM and higher density of eosinophil infiltration compared to those without OD [41]. More studies suggest that the extent of eosinophilic inflammation may directly and indirectly affect OD [60]. The direct impact is due to the degranulation proteins released by eosinophils, such as major basic protein (MBP), eosinophil peroxidase (EPX), eosinophil cationic protein (ECP) and eosinophil-derived neurotoxins (EDN), which can directly cause dysfunction and destruction of the cells in OE [60]. The indirect impact lies in the release of cytokines and chemokines by eosinophils, which can induce local inflammation, and cause damage to the OM [61, 62]. In addition, an eosinophilic biomarker Charcot Leyden crystal protein (CLC) was found in the upper turbinate of CRSwNP

patients, supporting the possibility that local eosinophilic influx in OC may be related to OD [63]. Studies have found that type 2 CRS is significantly associated with comorbidities such as allergic rhinitis, asthma, and olfactory loss [64, 65]. Due to the high aggregation of eosinophils and the mediation of specific cytokines (such as IL-5 and IL-13) [66], patients with type 2 CRS exhibit significant structural and functional impairment of the OM [41, 45, 67]. This damage compromises the integrity of OSNs, undermines the supportive role of olfactory epithelial cells, impairs the defense function of the nasal mucosal barrier, and impedes the transmission of olfactory signals, ultimately leading to severe OD.

Moreover, studies have shown that the intrabulbar neural circuits of OB in patients with CRS is significantly disordered due to inflammation, manifesting as atrophy of the OB's superficial layer [31], reduction of OSNs transmission under inflammation of OC, and reduced volume of the OB [8••] (Fig. 2). Interestingly, it was observed that OB can recover from atrophy once chronic inflammation subsides. However, the regeneration of OSNs was found to be incomplete [31, 35]. Gudziol, et al. found that the volume of OB in CRS patients significantly increased after 3 months of treatment and was significantly correlated with an improvement of odor threshold, confirming that the size of OB volume correlates with olfactory function [68]. However, whether the reduction in OB volume is the cause or result of OD remains to be further explored.

In addition, the structure and integrity of olfactory-related regions in the cerebral cortex of CRS patients are also important [69]. The gray matter density of olfactory related areas in the brain of CRS patients with severe OD decreases, including the rectus gyrus, medial orbital frontal gyrus, thalamus, and insula [69]. The decrease in gray matter density in these regions may be related to the neural mechanisms of OD that affects olfactory processing and perception. Nevertheless, our understanding of CRS related brain structural changes is still limited and further research is needed.

Assessment of OD in CRS Patients

Questionnaires

A questionnaire is a simple and effective tool for evaluating olfactory function, using personal self-reporting to gain a deeper understanding of a patient's level of OD and its impact on their QOL [70]. The Sino-Nasal Outcome Test-22 (SNOT-22) is a comprehensive questionnaire that evaluates nasal symptoms, olfactory function, emotional state, and sleep quality across 22 questions. Although the SNOT-22 questionnaire is one of the most widely used tools to describe sinonasal QOL in patients with CRS, it has only a single item dedicated to olfactory function [13]. Visual Analogue Scale (VAS) is an intuitive and accessible tool that enables participants to self-evaluate their olfactory function along a continuous scale [13]. The Questionnaire of Olfactory Disorders (QOD) is a widely used tool for evaluating the impact of OD on individual's QOL [70]. The Questionnaire of Olfactory Disorders-Negative Statements (QOD-NS) is a revised version of the QOD, which uses negative statements to reduce subjective biases in participant responses and improve the accuracy of evaluations. This adaptation has proven to have a strong correlation with CRS related OD [13]. However, some studies suggest that there may be a lack of direct correlation between changes in olfactory function and questionnaires [13], as the results may be easily influenced by the individual's psychological and emotional state [71].

Endoscopy Scale

Endoscopic scale is a reliable and intuitive assessment tool that can help clinicians quantify the severity of sinusitis symptoms and monitor the progression of the disease. Soler et al. proposed the Olfactory Cleft Endoscopy Scale (OCES), a scoring system that specifically focuses on the pathological status of OC [72]. As a tool specific to olfactory assessment, OCES provides additional information to traditional nasal endoscopy. Schlosser et al. further confirmed the correlation between OCES and the Sniffin' Sticks test as well as QOD-NS through a multicenter study [73]. This finding demonstrates the effectiveness of OCES in evaluating OD of CRS patients.

Psychophysical Tests

Psychophysical tests are designed to provide both qualitative and quantitative evaluations of olfactory function. The commonly used psychophysical tests include the Sniffin' Sticks test and the University of Pennsylvania Smell Identification Test (UPSIT), both of which are widely used to evaluate the OD of CRS patients [74, 75]. However, these tests may face challenges in cross-cultural applications, as odor identification tests rely on an individuals' previous experience with specific odors, which is often influenced by cultural backgrounds such as dietary habits, natural environment, and social customs [8••]. To overcome this limitation, researchers have developed olfactory recognition tests targeting different cultural groups. For example, in the United States, the most commonly used odor recognition test is UPSIT; in Spain, the Barcelona Smell Test-24 odors (BAST-24) is preferred; in Switzerland, the Smell Diskettes is widespread test; and in Japan, the Toyota & Takagi (T & T) Olfactometer has been extensively used [10•, 76]. Besides, Feng et al.

developed a smell recognition test specifically for the Chinese population (CSIT) [77]. Although there are some differences in the programs of these tests, the major difference lies in the odor settings, which vary depend on the regions. Currently, through continuous improvements, UPSIT has become one of the most widely used clinical evaluation tools globally, and has been validated in numerous studies in different countries [8••, 78].

Electrophysiology

Electrophysiological testing plays a crucial role in evaluating olfactory function, objectively assessing olfactory function by recording of electrical signals caused by olfactory stimuli. The Electro-olfactogram (EOG) and Olfactory Event-Related potentials (OERP) are commonly used methods that provide objective information about the olfactory conduction pathway and the CNS's processing of olfactory information. By combining the use of EOG and OERP, olfactory function can be comprehensively evaluated, from the primary responses of the OE to the advanced processing of the brain. However, these methods are relatively expensive and require specialized equipment and technical personnel to operate, which will limit their clinical application [60].

Imaging

Imaging examinations provide important diagnostic information when evaluating the OD of CRS patients. These methods enable doctors to visualize the structures of the nasal cavity, sinuses, and brain, thereby determine the underlying causes and the severity of OD. Both computed tomography (CT) and magnetic resonance imaging (MRI) attempted to evaluate the olfactory function of CRS patients. CT is a routine clinical examination for CRS, used to evaluate the severity of sinonasal mucosal inflammation and help to determine the severity of CRS [13, 76]. Research has found a correlation between the degree of sinus opacity and the severity of OD [79]. In CRSwNP patients, the correlation between OC opacity and olfactory function is stronger compared to adjacent sinus opacity [80]. MRI provides superior visualization of soft tissues compared to CT [8••]. Especially when investigating intracranial structures and pathology related to OD, MRI is the preferred diagnostic method. It plays a crucial role in visualizing brain structures, particularly those related to the olfactory system, and can provide detailed imaging of OB, olfactory tract, olfactory sulcus, and central olfactory projection areas [8••]. There is evidence to suggest that the size of OB on MRI is associated with olfactory loss in CRS patients [13]. However, MRI typically requires more clinic time, and the cost-effectiveness should also be considered [8••].

Treatment of OD in CRS Patients

Medications

The conventional treatment for CRS with OD includes intranasal and systemic corticosteroids [1••, 8••]. Intranasal corticosteroids and saline irrigation are preferred as initial treatments for CRS patients, while systemic corticosteroids can be a useful addition to intranasal corticosteroids treatment in patients with partially controlled or uncontrolled disease [1••, 22]. Studies have shown that oral corticosteroids were more effective than intranasal corticosteroids in improving patients' symptoms and olfactory function [81]. However, a meta-analysis revealed that although subjective improvement is observed with oral, topical, or combination steroid therapy, the improvement in objective olfactory outcomes was not significant [82]. Although medication may provide short-term relief, symptoms often recur rapidly once stopped. In addition to corticosteroids, other drugs such as phosphodiesterase inhibitors and intranasal calcium buffers have also been shown to improve OD [83, 84]. However, clinical evidence is still insufficient to support its application in the treatment of OD in CRS patients.

Surgery

When medical treatment fails and persistent symptoms occur, endoscopic sinus surgery (ESS) becomes the next treatment option for patients with CRS [1••, 4]. The surgery aims to remove pathological tissue from the sinuses, improve sinus ventilation and drainage, thereby reducing inflammation and improving OD. Meta-analyses shows that ESS has a positive impact on olfactory function in CRS patients, particularly those with severe nasal polyps [85, 86], and simultaneous nasal septoplasty can improve the likelihood of olfactory recovery [87]. However, the evaluation of olfactory improvement after ESS based on Sniffin's Sticks test has shown controversial results, which may be related to the severity of inflammation and damage to olfactory nerve epithelial cells [86]. Moreover, researchers have found that a considerable proportion of ESS do not alter olfactory outcomes and may even lead to olfactory imparirment. The study report revealed that the rate of postoperative anosmia may reach up to 19% [88]. Therefore, ESS is not recommended when OD is the only symptom, as its efficacy is difficult to predict [82].

Biologics

At present, several biologics have shown significant therapeutic effects in the treatment of CRSwNP, such as dupilumab (anti-IL-4Rα), omalizumab (anti-IgE), mepolizumab (anti-IL-5) and benralizumab (anti-IL-5R) [89, 90]. These drugs reduce inflammation, improve nasal congestion and OD, while dupilumab shows significant improvement in OD [82, 89–94]. Mullol et al. showed that even in patients who have previously undergone sinus surgery or systemic corticosteroid therapy,

Table 2 Summary of the references on the pathologic mechanisms of OD in CRS

Reference	Patients /Sample types	Methodology	Olfaction measure	Outcome/results
Histopathological study				
Yee et al. (2010) [41]	50 CRS	OE biopsies	NR	The extent of OM damage was related to the severity of OD, including normal pseudostratification, mixing of OE and goblet cells, squamous metaplasia, and erosion etc
Yee et al.(2009) [42]	54 CRS	Nasal biopsies	NR	The pathological changes of OM were associated with OD, such as goblet cell hyperplasia, squamous metaplasia, and erosion
Hauser et al. (2017) [39]	27 CRSsNP 32 CRSwNP	Ethmoid bulla tissue(obtained during ESS)	SIT-40	In CRSwNP, the increase of eosinophils in ethmoid bulla was related to OD
Hasegawa-Ishii et al. (2017) [34]	LPS-induced nasal inflammation mice	OE and OB	NR	Chronic nasal inflammation led to OB atrophy, which partially recovered after inflammation subsides, but the regeneration of OSNs may not have been complete
Chen et al. (2019) [37]	IOI mice	HBCs in OE	NR	Chronic Inflammation directed the HBCs to switch from neuroregeneration to immune defense through the NF-kB signaling pathway, resulting in OD
Rouyar et al.(2019) [38]	HDM and SEB sensitized CRS mice	OE	Observation of olfactory behavior, EOG	Elevated levels of IL-4, IL-5, and IL-13 in OE, as well as decreased levels of immature OSNs, were associated with OD
Turner et al.(2010) [50]	Unilateral olfactory bulbectomy on IOI mice	OE following TNF-alpha expression	NR	TNF-α inhibited the regeneration of OE by inhibiting the proliferation of basal progenitor cells and the production of immature OSNs
Zhao et al. (2014) [32]	29 CRS	CRS nasal cavity airflow and odorant absorption to the olfactory region which based on individual CT scans with CFD models	ODTs	CFD simulation revealed that conduction OD in CRS was significantly correlated with odor absorption in the olfactory region, MCA of the nasal cavity, and CT scores
Nishijima et al. (2018) [33]	Virtual nasal polyp models	all-olfactory model, preolfactory model, MM model, SM model generated from CT	NR	The location of NP significantly affected olfactory function, with polyps located anterior to the olfactory region having the greatest impact on olfactory function
Wu et al. (2018) [52]	31 CRSsNP 12 CRSwNP	Biomarkers in the OC and MM mucus	Validated SIT	Elevated levels of IL-2, IL-5, IL-6, IL-10, and IL-13 in OC mucus were associated with OD, especially in CRSwNP
Lavin et al. (2017) [63]	36 CRSwNP 63 CRSsNP	Biomarkers in tissue biopsies(ST, IT, NP)	Sniffin' Sticks, UPSIT	In CRSwNP, elevated expression of eosinophil marker CLC in ST was correlated with OD
Han et al. (2020) [51]	25 CRSsNP 46 CRSwNP	Type1/type 2 inflammatory cytokines in nasal mucus	Sniffin' Sticks	Levels of IFN-γ, IL-4, IL-5, GM-CSF, and IL-10 in OC mucus were significantly correlated with OD. In CRSsNP, OD was associated with TNF-α, while in CRSwNP, it was associated with IL-4 and IL-5

Table 2 (continued)

Reference	Patients /Sample types	Methodology	Olfaction measure	Outcome/results
Soler et al. (2020) [49]	37 CRSwNP 25 CRSsNP	Biomarkers in OC mucus	Sniffin' Sticks	10 proteins in OC mucus were significantly correlated with OD. In CRSwNP, this included CCL2, IL-5, IL-6, IL-13, IL-10, IL-9, TNF-α, CCL5, CCL11, while in CRSsNP, only CXCL5 showed correlation
Schlosser et al. (2016) [48]	15 CRSwNP 9CRSsNP	Biomarkers in OC mucus	Sniffin' Sticks	The level of IL-5 in OC mucus was negatively correlated with the olfactory scores in both CRSwNP and CRSsNP, while IL-6, IL-7, and VEGF-A were positively correlated with the olfactory scores in CRSwNP
Kanemitsu et al. (2020) [65]	including 20 with comorbid asthma	Sputum, nasal polyp and sinus tissue, FeNO	SNOT-22	In CRS, OD was associated with sputum eosinophil count. CRS complicated with asthma showed higher sputum eosinophils and FeNO, indicating poorer OD
Han et al. (2017) [69]	21 CRS	OB	Sniffin' Sticks	In CRS with severe OD, a decrease in GM was observed in the rectus gyrus, orbitofrontal cortex, thalamus, and insula, but the volume of OB remained unaffected

CCL = C–C motif chemokine ligand; CLC = charcot leyden crystal protein; CFD = computational fluid dynamics; CRS = chronic rhinosinusitis; CRSsNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyps; CT = computed tomography; EOGs = electroolfactogram; ESS = endoscopic sinus surgery; FeNO = fractional exhaled nitric oxide; GM = gray matter; GM-CSF = granulocyte–macrophage colony-stimulating factor; HBCs = horizontal basal cells; HDM = house dust mite; IFN = interferon; IL = interleukin; IM = inferior meatus; IOI = induced olfactory inflammation; IT = inferior turbinate; LPS = lipopolysaccharide; MCA = minimal cross-sectional area; MM = middle meatus; NF-kB = nuclear factor kappa-B; NP = nasal polyps; NR = not reported; OB = olfactory bulb; OC = olfactory cleft; OD = olfactory dysfunction; ODTs = odorant detection thresholds; OE = olfactory epithelium; OM = olfactory mucosa; SIT = Smell Identification Test; SIT-40 = 40-item Smell Identification Test; SEB = dtaphylococcus aureus enterotoxin B; SM = superior meatus; ST = superior turbinate; SNOT-22 = 22-item Sinonasal Outcome Test; TNF-α = tumor necrosis factor alpha; UPSIT = University of Pennsylvania Smell Identification Test

dupilumab can rapidly and sustainably improve olfactory function [93]. However, OD may not necessarily be the first symptom that needs improvement [82]. Thus, olfactory function is not recommended as an early indicator of response to biologics. The early or late response in olfaction is related to the degree of inflammatory changes of the olfactory epithelium, which largely varies among CRS patients [82].

Olfactory Training (OT)

OT is a method that enhances olfactory ability through repeated exposure to different odors. Previous studies have confirmed that OT is beneficial for patients with post-traumatic OD (PTOD) and post-infectious OD (PIOD) [8••, 95], as it can promote the recovery of olfactory function by regulating the mechanism of brain structure. [96]. Hummel et al. found that after OT, patients with post-infectious and idiopathic loss of smell had higher EOG records in OE, indicating that OT not only affects central olfactory processing but also the recovery of OE [97]. However, the effectiveness of OT treatment for CRS related OD is still controversial. Recently, Park et al. found that a 12-week short-term OT program has a positive effect on the recovery of olfactory function in CRS patients after sinus surgery, especially in improving sensory-neural olfactory impairment [98]. However, the method mentioned in this study has not been widely validated. The advantage of OT lies in its simplicity, reasonable cost-effectiveness, and ease of self-management. As a potential treatment option, its clinical efficacy and long-term outcomes for CRS still need further exploration and verification [8••, 99].

Others

Recently, scientists are exploring various innovative therapies. Stem cell therapy is a new approach aimed at restoring olfactory function by transplanting stem cells to repair damaged olfactory tissue [8••, 100]. Additionally, OB stimulation therapy attempts to restore olfaction by directly stimulating the olfactory nerves [8••, 101]. There are also various pharmacological treatments, including vitamin A, platelet-rich plasma, omega-3 fatty acids, N-acetylcysteine, and gene therapy [8••, 92]. These treatment methods have not yet been applied to CRS related OD patients, and strict clinical trials need to be conducted to fully evaluate the safety and effectiveness of these therapies.

Conclusion

An increasing number of studies have revealed the diverse pathological mechanisms of OD in CRS patients. Inflammatory factors play a crucial role in the development of OD in patients with CRS. Usually, the deterioration of OD in CRS is associated with type 2 inflammation. Generally, the evaluation methods for OD mainly include three different categories, including self-reported assessments based on questionnaires or scales, psychophysical tests, and electrophysiological or imaging assessments. A series of treatment methods, including medication, surgical intervention, and OT, have shown certain benefits in improving olfactory function of CRS patients. In addition, emerging biologic therapies provide new treatment options for CRS patients with OD. Nevertheless, further studies need to elucidate the optimal indications and long-term outcomes of these treatment approaches.

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Declarations

Competing Interests The authors declare no competing interests.

Conflict of Interest The authors declare that they have no competing interests.

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• Of importance
•• Of major importance

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