The Olfactory Cleft Endoscopy Scale: a multi-institutional validation study in chronic rhinosinusitis*

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Abstract

Background: Olfactory dysfunction (OD) associated with chronic rhinosinusitis (CRS) remains quite challenging. Instruments to precisely assess olfactory cleft anatomy and their association with olfaction are needed.

Methods: The olfactory cleft endoscopy scale (OCES) was used to assess the olfactory cleft in healthy control subjects and a cohort of patients with CRS. Psychophysical and psychosocial olfactory function were assessed and correlations with OCES scores were measured.

Results: Control subjects and subjects with CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) were enrolled. OCES correlated with both psychophysical and psychosocial olfaction, as measured by threshold, discrimination and identification (TDI) scores and Questionnaire on Olfactory Disorders (QOD-NS) scores for all case and control subjects combined. OCES improved in both CRS groups postoperatively with the highest correlation seen in postoperative olfaction in CRSwNP patients. CRS patients who achieve near perfect OCES and sinus endoscopy scores after surgery have olfactory metrics that are indistinguishable from controls regardless of polyp status.

Conclusions: The OCES is a valid olfactory-specific measure that demonstrates strong validity and provides complimentary information to traditional sinus endoscopy to aid in our understanding of OD associated with CRS.

Key words: Sinusitis, endoscopy, olfaction, polyps, validation

Introduction

Olfactory dysfunction (OD) is commonly reported in chronic rhinosinusitis (CRS). While medical and surgical treatments improve sinus-specific measures in most patients, there are still wide variations in olfactory outcomes. Most CRS-specific endoscopic measures assess the paranasal sinuses, and correlate reasonably well with sinus-specific quality of life (QOL). For example, post-operative Lund-Kennedy endoscopy scoring (LKES) of the sinuses at 6 months correlates with post-operative sinus-specific QOL[(1)]. Those with normal or near-normal sinus endoscopy had near normal SinoNasal Outcome Test (SNOT-22) scores. This is logical because resolution of visible inflammation in the sinuses after surgery should be a strong signal of disease control and hence symptom control. However, when examining objective sinus-specific metrics, such as LKES, the correlation to olfactory outcomes weakens. This weaker correlation between sinus-specific metrics and olfactory outcomes may be secondary to disease processes that affect the olfactory cleft (OC) independently of those impacting the sinuses. This has led to investigations studying olfactory-specific endoscopy, imaging, and cytokine expression[(2-6)].

Given the potential independent nature of sinus inflammation

and OC inflammation, we developed an OC endoscopy scale (OCES). Similar to LKES, the OCES specifically measures polyps, edema, mucus, crusting and scar[3], but does so in the OC, rather than the sinuses. The OCES was initially validated in a single institution cohort and shown to correlate to psychophysical and psychosocial olfactory measures. This study was designed to further validate the OCES in a prospective multi-institutional CRS cohort, compare OCES to control subjects, and assess its utility in understanding OD after surgery in patients with CRS.

Materials and methods

Sample study population with CRS

Case subject enrollment originated from an observational, prospective research investigation of human subjects funded by the National Institute on Deafness and Other Communication Disorders. Case study participants were recruited from patient populations presenting to academic, rhinology centres: Oregon Health and Science University (OHSU, Portland, OR), Medical University of South Carolina (MUSC, Charleston, SC), University of Utah (Salt Lake City, UT), University of Colorado (Aurora, CO), and University of Virginia (UVA, Charlottesville, VA). Adult study participants (> 18 years of age) with medically recalcitrant CRS, with nasal polyposis (CRSwNP) or without nasal polyposis (CRSsNP), were enrolled following criteria established by current clinical practice guidelines of the American Academy of Otolaryngology-Head and Neck Surgery[7]. All case subjects were deemed surgical candidates for endoscopic sinus surgery (ESS). Patients provided written, informed consent after baseline enrollment meetings.

Following surgical counseling and prior to study enrollment, case subjects voluntarily elected ESS as a treatment modality for intervention for sinonasal symptoms. Intraoperative judgement of each enrolling physician dictated surgical extent. Middle turbinates were medialized as part of standard surgical procedures, however, suturing was not performed. Middle turbinates were resected at the discretion of the treating surgeon. Postoperative medical therapy consisted of topical steroid therapy in all cases and systemic steroid therapy was tailored to the extent of inflammation noted during postoperative clinical visits per the judgement of the treating surgeon.

Sample study population without CRS

Control study subject data originated from a community-based population of healthy subjects without history of CRS, previous ESS or any olfactory complaints. Volunteers were recruited locally using advertisements, word-of-mouth, and self-referral techniques. Control participants were prospectively interviewed and enrolled on a voluntary basis. The Institutional Review Board affiliated with all enrollment locations approved study protocols.

Exclusion criteria

Case and control study subjects were excluded due to a known history of comorbid conditions associated with increased prevalence of OD at the time of enrollment including: Sarcoidosis, granulomatosis polyangitis, dementia, aphasia, or Alzheimer's disease, other non-specified neurocognitive disorders, Parkinson's disease, major head trauma / traumatic brain injury, and patients on immunosuppressive medications. Additionally, due to the need to perform sinonasal endoscopy with minimal risk, control subjects with a history of vasovagal syncope and/or adverse reaction to local anesthetics or decongestants, such as lidocaine and phenylephrine were excluded.

Clinical measures of disease severity

Subjects provided a medical and social history as well as descriptions of current therapeutic regimens. Clinical measures of disease severity were collected. Paranasal sinuses were evaluated for all patients using rigid endoscopy and graded using LKES which quantifies visualized pathologic states within the paranasal sinuses (score range: 0-20)[8]. Pathology of the OC was evaluated simultaneously and graded using the OCES[3]. The OCES quantifies the severity of pathologic attributes evident in the OC from 0 to 2 points, including: discharge, nasal polyposis, edema, crusting, and scarring (score range: 0-20) similar to LKES. Higher scores on both staging systems indicate worse disease severity. Postoperative OCES measures were collected on case subjects, if possible, approximately 6 months following ESS during routine clinical follow-up appointments. Diagnostic categorizations of LKES and OCES total scores included disease severity designations of "near perfect" (OCES or LKES<2), "moderate" (OCES or LKES: 3-5), and "high" (OCES or LKES: >6), similar to prior reports[3]. OCES and LKES were always performed after application of topical anesthetic and vasoconstrictor.

Measures of olfactory function

Subjects completed a comprehensive evaluation of bilateral olfactory function using Sniffin' Stick pens (Burghart Messtechnik, Wedel, Germany) which evaluate three separate domains of olfactory function including: odorant threshold (score range: 1-16), odorant discrimination (score range: 0-16), and odorant identification (score range: 0-16)[9, 10]. Odorant threshold (n-butanol target) was evaluated in a 'staircase procedure' using pen triplets in which odorant thresholds are detected on a continuum of dilution steps until the weakest odorant can be accurately distinguished from two blanks offered in random sequence. Odorant discrimination was conducted using a sequence of presented pen triplets in which two pens have the same odorant. Study participants were directed to identify the single, remaining pen with a different odorant from the sequence. Odorant identification was evaluated using 16 pens containing common odorants presented individually. Respondents were directed to select the

correct odorant from four multiple-choice options. Correctly identified threshold (T), discrimination (D), and identification (I) scores, as well as a composite TDI total score, are summarized from item responses (score range: 1-48) with higher scores reflecting superior overall olfactory function. Case subjects were also asked to complete Sniffin' Stick testing ~6 months postoperatively, if possible, during routine clinical follow-up appointments.

Patient Reported Outcome Measures (PROMs)

CRS study participants completed two self-administered PROMs during baseline enrollment meetings. First, the SNOT-22 is a validated, self-administered survey designed to capture symptom severity associated with sinonasal disorders with minimal time burden. Symptom severity is measured using Likert-scales which indicate: 0= "No problem", 1= "Very mild problem", 2= "Mild or slight problem", 3= "Moderate problem", 4= "Severe problem" and 5= "Problem as bad as it can be". Total scores for the SNOT-22 are summarized from all item responses (score range: 0-110) with higher scores indicating worse overall symptom severity. Of additional interest to this investigation, the SNOT-22 contains one survey item that enquires about symptom severity associated with a respondent's "Sense of smell / taste". Responses to that single, olfactory-specific item and SNOT-22 total scores were targeted for this investigation.

Secondly, the Questionnaire of Olfactory Dysfunction contains 17 negatively termed item statements (QOD-NS) designed to evaluate the perceived impact of olfactory dysfunction on respondent's daily function. The QOD-NS is a validated, olfactory-specific survey which summarizes Likert scale responses from 0 ("Disagree") to 3 ("Agree") whereas higher total scores (score range: 0 – 51) represent worse overall olfactory impairment[11]. Case subjects were also asked to complete both surveys ~6 months postoperatively. Given that nasal polyp grade is included in both LKES and OCES, patients with CRS were divided into CRSsNP and CRSwNP for analysis throughout the study. Control subjects only completed QOD-NS PROMs.

Biostatistical analyses and data management

Data security was ensured through the assignment of unique study identification numbers for study participants and removal of all protected health information prior to data entry using a centralized database (Access; Microsoft Corporation; Redmond, WA). Data visualization was created with R using the packages ggplot, scatterplot3d, and plot3d (R Core Team, Vienna, Austria). Descriptive and statistical comparisons were completed using SPSS software (version 26.0; IBM Corporation, Armonk, NY). Statistical analyses were guided after an evaluation of all scaled measures for assumptions of normality and linearity. Omnibus statistics evaluated average differences between CRSsNP, CRSwNP, and control subjects using either one-way analysis of variance (F-test statistics), with adjustment for multiple comparisons using Bonferroni corrections, or chi-square (χ^2) testing using 3x2 contingency tabling. Significant global differences between case and control subjects justified odds ratio (OR) calculated as basic measures of relative risk.

Spearman's rank correlation coefficients (R) were used to evaluate linear associations between OCES, Sniffin' Sticks, and QOD-NS scores. Average within-subject differences over time were also evaluated using matched paired samples t-testing for all olfactory metrics for CRSsNP and CRSwNP case subjects. Sample size variation exists throughout the analysis of postoperative data due to incomplete patient follow-up. Descriptive statistics, 95% confidence intervals (CI), and type-I error probabilities (p-values) are provided where appropriate.

Results

Final study cohorts

A total of 405 study participants enrolled in the study between November, 2016 and February, 2020 consisting of 114 (28%) of subjects with CRSsNP, 127 (31%) of subjects with CRSwNP, and 164 (41%) control subjects. For study participants with CRS electing ESS (n=241), a total of 157 (65%) provided some measure of postoperative follow-up an average of 6.02 [SD±1.9] months after surgery. Participant demographics, comorbid conditions, clinical measures of disease severity, average measures of olfactory function and PROM scores are described in Table 1. Sample size variation is due to incomplete data collection. Differences in all descriptive characteristics between case subjects with either CRSsNP and CRSwNP and controls were evaluated using omnibus statistics. No statistically significant differences between control and either CRS subgroup were found across average age, years of education, comorbid diabetes, or reported alcohol use. Bivariate comparisons identified that control subjects had a significantly higher odds of being female compared to CRSwNP (OR=1.77; 95% CI: 1.11-2.83; p=0.017) but a reduced odds of being white/Caucasian compared to either CRSsNP (OR=0.14; 95% CI: 0.06-0.34; p<0.001) or CRSwNP (OR=0.47; 95% CI: 0.26-0.84; p=0.010). Compared to either CRSsNP or CRSwNP, control subjects also had a significantly lower prevalence of the majority of comorbid conditions assessed during baseline enrollment meetings.

Baseline CRS and olfactory-specific metrics

OCES correlated with both psychophysical and psychosocial olfaction, as measured by Sniffin' Sticks total scores (R= -0.533, p<0.001; n=311) and QOD-NS scores (R=0.388, p<0.001; n=309) for all case and control subjects combined.

After adjustment for multiple comparisons, control subjects were found to have lower average OCES scores, lower QOD-NS scores, and higher Sniffin' Stick threshold scores compared to both CRSsNP and CRSwNP (Table 1, p<0.007). Control subjects

Table 1. Descriptive characteristics and global comparisons of final study cohorts at enrollment.

Demographics		Case Subjects with CRSsNP (N=114)	Case Subjects with CRSwNP (N=127)	Control Subjects (N=164)	Omnibus test statistic	Omnibus p-value
Age in years	Mean ± SD	48.4 ± 17.3	49.0 ± 15.2	51.5 ± 17.3	F= 1.34	0.263
Males	N (%)	55 (48%)	65 (51%)	61 (37%)	χ2= 6.48	**0.039**
Females		59 (52%)	62 (49%)	103 (63%)		
White/Caucasian		107 (94%)	106 (84%)	117 (71%)	χ2= 25.21	**<0.001**
African American		4 (4%)	15 (12%)	38 (23%)	χ2= 22.00	**<0.001**
Asian		1 (1%)	3 (2%)	4 (2%)	χ2= 0.98	0.613
Hispanic/Latino ethnicity		9 (8%)	7 (6%)	6 (4%)	χ2= 2.35	0.309
Comorbidity						
Nasal polyposis		0 (0%)	127 (100%)	0 (0%)	χ2= 405.00	**<0.001**
Previous sinus surgery / ESS		36 (32%)	80 (63%)	0 (0%)	χ2= 139.63	**<0.001**
Asthma		47 (41%)	70 (55%)	14 (9%)	χ2= 76.69	**<0.001**
Diabetes mellitus (Type I/II)		10 (9%)	8 (6%)	15 (9%)	χ2= 0.86	0.651
Depression (history/self-reported)		34 (30%)	33 (26%)	27 (17%)	χ2= 7.54	**0.023**
Smoking / tobacco use (current)		5 (4%)	3 (2%)	19 (12%)	χ2= 6.29	**0.043**
Smoking / tobacco use (former)		25 (22%)	37 (29%)	0 (0%)	χ2= 48.17	**<0.001**
Alcohol use (current)		53 (47%)	69 (54%)	99 (60%)	χ2= 5.48	0.064
Positive allergy test (mRast/skin prick)		48 (42%)	74 (58%)	38 (23%)	χ2= 36.88	**<0.001**
GERD		38 (33%)	34 (27%)	18 (11%)	χ2= 21.67	**<0.001**
Autoimmune disease		16 (14%)	12 (9%)	5 (3%)	χ2= 11.06	**0.004**
Oral corticosteroid use (past 30 days)		26 (23%)	33 (26%)	1 (1%)	χ2= 44.55	**<0.001**
Clinical Measures of Disease Severity		**(n=112)**	**(n=126)**	**(n=123)**		
Lund-Kennedy endoscopy score		4.9 ± 2.7	9.4 ± 3.1	----	t= -12.15	**<0.001**
Olfactory cleft endoscopy score		2.1 ± 2.4	6.6 ± 3.8	0.6 ± 1.1	F= 152.50	**<0.001**
Measures of Olfactory Function		**(n=114)**	**(n=127)**	**(n=164)**		
Sniffin' Sticks total score		27.5 ± 7.0	17.5 ± 8.9	28.8 ± 7.0	F= 87.09	**<0.001**
Threshold score		5.0 ± 2.9	2.9 ± 2.8	6.1 ± 2.7	F= 48.22	**<0.001**
Discrimination score		11.0 ± 2.9	7.4 ± 3.1	10.9 ± 2.7	F= 64.66	**<0.001**
Identification score		11.5 ± 3.0	7.2 ± 4.2	11.8 ± 2.8	F= 77.32	**<0.001**
Patient Reported Outcome Measures		**(n=114)**	**(n=126)**	**(n=163)**		
SNOT-22 total score		45.6 ± 19.5	52.2 ± 21.4	----	t= -2.48	**0.014**
Item: "Sense of smell / taste"		2.4 ± 1.8	3.8 ± 1.6	----	t= -6.20	**<0.001**
QOD-NS total score		10.3 ± 10.1	17.3 ± 11.1	4.4 ± 6.9	F= 68.33	**<0.001**

CRSsNP, chronic rhinosinusitis without nasal polyposis; CRSwNP, chronic rhinosinusitis with nasal polyposis; SD, standard deviation; N, sample size; ESS, endoscopic sinus surgery; OSA, obstructive sleep apnea; GERD, gastroesophageal reflux disease; SNOT-22, 22-item Sinonasal Outcome Test survey; QOD-NS, Questionnaire of Olfactory Dysfunction-negative statements. F, F-test statistic associated with one-way analysis of variance; t, independent sample t-test statistic; χ2, chi-square test statistic with 2x2 or 3x2 contingency tables.

were also found to have significantly better mean Sniffin' Stick total scores, olfactory discrimination scores, and olfactory identification scores but only when compared to subjects with CRSwNP (p<0.001).

Bivariate comparisons between CRSsNP and CRSwNP found that study subjects with nasal polyposis had significantly worse average measures of OCES (t= -9.61; Δ=4.45; 95% CI: 3.54-5.36; p<0.001), Sniffin' Sticks total scores (t= 9.63; Δ=10.00; 95% CI: 7.96-12.05; p<0.001), olfactory threshold (t= 5.91, Δ=2.14; 95% CI: 1.43-2.86; p<0.001), olfactory discrimination (t= 9.09, Δ=3.54; 95% CI: 2.78-4.31), olfactory identification scores (t= 9.28; Δ=4.33; 95% CI: 3.41-5.25; p<0.001), and QOD-NS (t= -5.12;

Table 2. Preoperative associations between endoscopic grading and olfactory metrics.

	CRSwNP preop		CRSsNP preop	
	OCES	LKES	OCES	LKES
	R (p-value)	R (p-value)	R (p-value)	R (p-value)
Sniffin' Sticks total	**-0.270 (p=0.008)**	**-0.330 (p<0.001)**	-0.060 (p=0.570)	**-0.185 (p=0.050)**
Threshold score	**-0.349 (p=0.001)**	**-0.294 (p=0.001)**	-0.122 (p=0.243)	**-0.198 (p=0.036)**
Discrimination score	-0.168 (p=0.104)	**-0.266 (p=0.003)**	0.040 (p=0.701)	-0.069 (p=0.471)
Identification score	**-0.238 (p=0.020)**	**-0.340 (p<0.001)**	-0.121 (p=0.249)	-0.179 (p=0.059)
SNOT-22 total score	0.036 (p=0.733)	-0.014 (p=0.873)	-0.056 (p=0.598)	-0.020 (p=0.837)
Item: "Sense of smell/taste"	0.148 (p=0.153)	**0.210 (p=0.018)**	0.151 (p=0.150)	0.037 (p=0.698)
QOD-NS total score	-0.013 (p=0.904)	0.002 (p=0.981)	0.122 (p=0.247)	0.022 (p=0.821)

CRSsNP, chronic rhinosinusitis without nasal polyposis; CRSwNP, chronic rhinosinusitis with nasal polyposis; SNOT-22, 22-item Sinonasal Outcome Test survey; QOD-NS, Questionnaire of Olfactory Dysfunction-negative statements; R, Spearmans rank correlation coefficient.

Table 3. Changes in olfactory metrics after ESS.

CRSsNP	N	Preoperative	Postoperative	Abs. Change	95% CI	Test statistic	p-value
		Mean [±SD]	Mean [±SD]	Mean [±SD]			
OCES	42	2.4 [±2.5]	1.0 [±2.2]	1.5 [±2.7]	0.6 – 2.3	3.43	**0.001**
LKES	53	5.5 [±2.6]	2.8 [±3.5]	2.6 [±3.6]	1.6 – 3.6	5.24	**<0.001**
Sniffin' Sticks total score	53	26.5 [±7.2]	27.7 [±8.0]	1.2 [±7.6]	-0.9 – 3.3	-1.15	0.257
Threshold score	53	4.4 [±3.1]	4.9 [±3.2]	0.5 [±4.0]	-0.6 – 1.6	-1.00	0.344
Discrimination score	53	10.8 [±3.2]	11.1 [±3.2]	0.3 [±3.3]	-0.6 – 1.2	-0.71	0.478
Identification score	53	11.4 [±2.9]	11.7 [±3.2]	0.4 [±2.8]	-0.4 – 1.1	-0.93	0.356
SNOT-22 total score	68	44.2 [±20.1]	23.4 [±18.1]	20.8 [±22.1]	15.4 – 26.1	7.75	**<0.001**
Item: "Sense of smell / taste"	68	2.3 [±1.8]	1.4 [±1.6]	0.9 [±1.8]	0.4 – 1.3	4.05	**<0.001**
QOD-NS total score	67	9.5 [±9.5]	5.3 [±7.3]	4.2 [±7.8]	2.3 – 6.1	4.39	**<0.001**
CRSwNP	**N**	**Preoperative**	**Postoperative**	**Abs. Change**	**95% CI**	**Test statistic**	**p-value**
		Mean [±SD]	Mean [±SD]	Mean [±SD]			
OCES	48	6.6 [±3.6]	4.0 [±4.2]	2.6 [±4.8]	1.2 – 4.0	3.81	**<0.001**
LKES	76	9.2 [±3.4]	4.6 [±3.6]	4.6 [±4.5]	3.5 -5.6	8.77	**<0.001**
Sniffin' Sticks total score	66	18.8 [±9.3]	24.3 [±8.7]	5.6 [±7.9]	3.6 – 7.5	5.75	**<0.001**
Threshold score	66	3.2 [±3.0]	4.1 [±3.0]	0.9 [±2.8]	0.2 – 1.6	2.63	**0.011**
Discrimination score	66	7.7 [±3.1]	10.1 [±3.5]	2.4 [±3.8]	1.5 – 3.4	5.23	**<0.001**
Identification score	66	7.9 [±4.3]	10.1 [±3.6]	2.2 [±3.5]	1.4 – 3.1	5.13	**<0.001**
SNOT-22 total score	88	50.7 [±20.5]	23.9 [±20.4]	26.8 [±17.8]	23.0 – 30.6	14.12	**<0.001**
Item: "Sense of smell / taste"	88	3.5 [±1.7]	2.2 [±1.7]	1.4 [±2.1]	0.9 – 1.8	6.12	**<0.001**
QOD-NS total score	87	15.5 [±10.5]	9.1 [±8.2]	6.4 [±8.9]	4.5 – 8.3	6.73	**<0.001**

CRSsNP, chronic rhinosinusitis without nasal polyposis; CRSwNP, chronic rhinosinusitis with nasal polyposis; SD, standard deviation; N, sample size; SNOT-22, 22-item Sinonasal Outcome Test survey; QOD-NS, Questionnaire of Olfactory Dysfunction-negative statements. OCES, olfactory cleft endoscopy score; LKES, Lund-Kennedy endoscopy score; CI, confidence interval; test statistic = matched paired samples t-test.

Δ=7.06; 95% CI: 4.35-9.77; p<0.001).

Associations with preoperative endoscopy scoring for CRSsNP and CRSwNP

Initial analyses aimed to identify differences in preoperative clinical measures of disease severity associated with either the sinuses or the OC. Spearman's rank correlations between OCES, LKES, scaled measures of olfactory function, and PROMs are

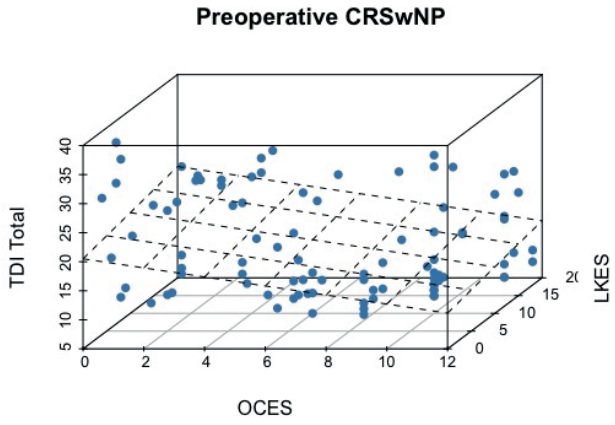

Figure 1. Three dimensional scatterplot of preoperative OCES, LKES, and TDI, with added regression plane, for patients with CRSwNP. This demonstrates the differing relationships of OCES and LKES with TDI, particularly in CRSwNP patients who have the most smell loss.

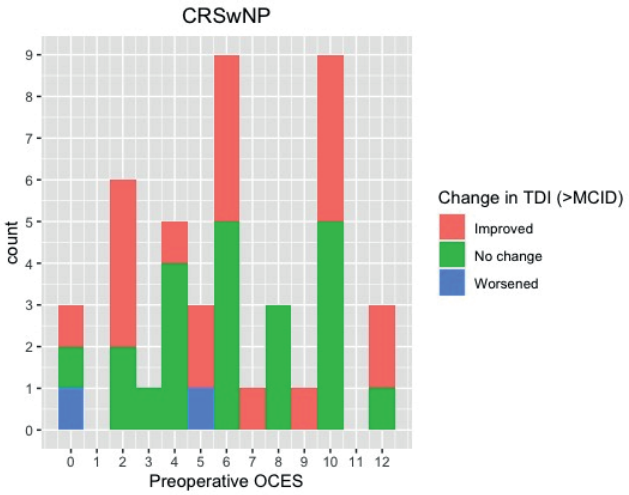

Figure 2. Stacked histogram of preoperative OCES for patients with CRSwNP, categorized by change in TDI of at least 5.5 points, the minimal clinically important difference (MCID) for this test. Improvement appears similar across the spectrum, suggesting that the entire range of preoperative OCES still maintains the possibility for olfactory improvement after treatment.

described in Table 2 for independent groups of CRSsNP and CRSwNP.

Preoperative OCES in CRSwNP patients was found to weakly correlate with Sniffin' Stick total, threshold and identification domain scores, but did not correlate with any olfactory metrics in CRSsNP. Preoperative LKES in CRSwNP patients correlated with all measures of olfactory function, and the olfactory-specific survey item of the SNOT-22 with larger magnitudes of correlation compared to all significant associations found in CRSsNP. Figure 1 demonstrates the relationship between preoperative TDI, OCES and LKES for CRSwNP patients.

Responsiveness of OCES to surgery

Table 3 demonstrates response of various olfactory metrics 6 months after surgical intervention. OCES improved in both CRSsNP (mean change 1.5 ± 2.7) and CRSwNP (mean change 2.6 ± 4.8), indicating responsiveness to change postoperatively. In CRSwNP, all other measures of olfaction also improved. Figure 2 demonstrates that patients with CRSwNP are able to achieve an MCID in TDI scores across the spectrum of preoperative OCES scores. Psychophysical measures of olfaction using Sniffin' Sticks did not improve significantly in CRSsNP, however QOD-NS did, suggesting that OCES and QOD-NS may be detecting subtle changes not measured by objective olfactory testing.

Associations with postoperative endoscopy scoring for CRSsNP and CRSwNP

Further analyses aimed to identify potential associations between postoperative endoscopy and 6 month postoperative clinical measures of olfactory function. Spearman's rank correlations between LKES, OCES, scaled measures of olfactory function, and PROMs are again described in Table 4.

In postoperative CRSwNP patients, OCES was found to significantly correlate with Sniffin' Stick total, threshold, discrimination, and identification domain scores, as well as all PROM scores, and all correlations were stronger than those noted with LKES. In postoperative CRSsNP patients, OCES only correlated with SNOT-22 measures, but in this group it also correlated more strongly than LKES.

Postoperative endoscopy and olfaction in patients with CRSsNP

We then analyzed postoperative patients by categorizing them into broad clinical groups based upon OCES and LKES as previously described[1, 3]. In CRSsNP, we are able to achieve near perfect OCES in 92% of patients (Table 5). Among these patients with near perfect OCES, 31% (14/45) still have moderate or severe sinus inflammation as assessed by LKES, but it appears that Sniffin' Sticks scoring is only impacted when sinus inflammation becomes severe.

Postoperative endoscopy and olfaction in patients with CRSwNP

In CRSwNP, we achieved near perfect OCES in 62% of patients (Table 6), yet even in these patients with near perfect OCES and LKES, there was still persistent hyposmia (mean Sniffin' Sticks total score: 27.6). In those with near perfect OCES, moderate or severe sinus inflammation persists in 37% (16/43), but appears to have minimal impact upon olfaction. On the other hand, 53% (37/70) of patients had moderate or severe inflammation at both anatomic sites and Sniffin' Sticks scores were low. Figure 3 demonstrates the distribution of postoperative patients categorization based upon OCES, LKES and TDI.

Table 4. Postoperative associations between endoscopy grading and olfactory metrics.

	CRSwNP postop		CRSsNP postop	
	OCES	LKES	OCES	LKES
	R (p-value)	R (p-value)	R (p-value)	R (p-value)
Sniffin' Sticks total	**-0.482 (p<0.001)**	**-0.368 (p=0.003)**	-0.163 (p=0.295)	-0.125 (p=0.396)
Threshold score	**-0.425 (p=0.001)**	**-0.377 (p=0.002)**	-0.224 (p=0.150)	-0.262 (p=0.072)
Discrimination score	**-0.356 (p=0.006)**	**-0.215 (p=0.090)**	-0.073 (p=0.641)	-0.068 (p=0.646)
Identification score	**-0.409 (p=0.001)**	**-0.281 (p=0.026)**	-0.055 (p=0.724)	-0.083 (p=0.576)
SNOT-22 total score	**0.495 (p<0.001)**	**0.343 (p=0.003)**	**0.335 (p=0.021)**	**0.292 (p=0.036)**
Item: "Sense of smell/taste"	**0.452 (p<0.001)**	**0.334 (p=0.004)**	**0.311 (p=0.031)**	**0.281 (p=0.042)**
QOD-NS total score	**0.401 (p=0.001)**	**0.305 (p=0.010)**	0.219 (p=0.144)	0.128 (p=0.372)

CRSsNP, chronic rhinosinusitis without nasal polyposis; CRSwNP, chronic rhinosinusitis with nasal polyposis; SNOT-22, 22-item Sinonasal Outcome Test survey; QOD-NS, Questionnaire of Olfactory Dysfunction-negative statements. R, Spearmans rank correlation coefficient; OCES, olfactory cleft endoscopy score; LKES, Lund-Kennedy endoscopy score.

Table 5. Comparison of postoperative disease severity designations as indicated by OCES and LKES in patients with CRSsNP (N=49).

LKES	OCES						Totals
	Near perfect		Moderate		High		
	N(%)	TDI Mean [±SD]	N(%)	TDI Mean [±SD]	N(%)	TDI Mean [±SD]	
Near perfect	31 (63%)	28.5 [±5.8]	0 (0%)	-	0 (0%)	-	31 (63%)
Moderate	11 (22%)	28.9 [±8.6]	1 (2%)	-	0 (0%)	-	12 (24%)
High	3 (6%)	19.1 [±14.9]	1 (2%)	-	2 (4%)	-	6 (12%)
Totals	45(92%)		2 (4%)		2 (4%)		49

CRSsNP, chronic rhinosinusitis without nasal polyposis; N, sample size; OCES, olfactory cleft endoscopy score; LKES, Lund-Kennedy endoscopy score; TDI, Threshold, Discrimination, Identification summarized scores of Sniffin' Sticks testing.

Table 6. Comparison of postoperative disease severity designations as indicated by OCES and LKES in patients with CRSwNP.

LKES	OCES						Totals
	Near perfect		Moderate		High		
	N(%)	TDI Mean [±SD]	N(%)	TDI Mean [±SD]	N(%)	TDI Mean [±SD]	
Near perfect	27 (39%)	27.6 [±7.3]	0 (0%)	-	0 (0%)	-	27
Moderate	12 (17%)	26.9 [±7.0]	4 (6%)	15.9 [±11.1]	1 (1%)	-	17
High	4 (6%)	24.4 [±3.0]	6 (9%)	30.3 [±6.36]	16 (23%)	18.0 [±9.0]	26
Totals	43 (62%)		10 (15%)		17 (24%)		70

CRSwNP, chronic rhinosinusitis with nasal polyposis; N, sample size; OCES, olfactory cleft endoscopy score; LKES, Lund-Kennedy endoscopy score; TDI, Threshold, Discrimination, Identification summarized scores of Sniffin' Sticks testing.

Outcomes of patients who achieve near perfect postop endoscopy

We then further examined olfaction in patients who had near perfect OCES and LKES. In CRSsNP, these patients have persistent hyposmia (mean Sniffin' Sticks total score: 28.5) despite achieving endoscopic control of both sinuses and OC. As seen in Table 7, olfactory metrics in CRSsNP patients with near perfect endoscopy are not significantly different from control subjects. Again, we further examined olfaction in CRSwNP patients who had near perfect OCES and LKES postoperatively. These patients

Table 7. Comparison of olfactory metrics between control subjects and CRS patients achieving near perfect OCES and LKES postoperatively.

Postoperative measures	Control Subjects (n=164)	CRSwNP with postoperative normal LKES and OCES (n=27)	Difference between CRSwNP and control (Δ)	95% CI	CRSsNP with postoperative normal LKES and OCES (N=31)	Difference between CRSsNP and control (Δ)	95% CI
	Mean [±SD]	Mean [±SD]	Mean [±SE]		Mean [±SD]	Mean [±SE]	
OCES	0.6 [±1.1]	0.5 [±0.8]	0.1 [±0.2]	-0.4 – 0.5	0.2 [±0.6]	0.4 [±0.2]	0.1 – 0.7
Sniffin' Sticks total	28.8 [±7.0]	27.6 [±7.3]	1.2 [±1.5]	-1.8 – 4.2	28.5 [±5.8]	0.2 [±1.4]	-2.6 – 3.0
Threshold	6.1 [±2.7]	5.4 [±3.1]	0.6 [±0.6]	-0.6 – 1.8	5.2 [±2.5]	0.9 [±0.5]	-0.2 – 1.9
Discrimination	10.9 [±2.7]	11.0 [±2.7]	0.1 [±0.6]	-1.2 – 1.1	11.4 [±2.4]	0.5 [±0.5]	-1.6 – 0.6
Identification	11.8 [±2.8]	11.2 [±3.1]	0.6 [±0.6]	-0.6 – 1.8	11.9 [±2.7]	0.1 [±0.6]	-1.2 – 1.0
SNOT-22 total	----	17.1 [±17.6]	----	----	24.4 [±18.3]	----	----
Item: "Sense of smell / taste"	----	1.8 [±1.6]	----	----	1.3 [±1.6]	----	----
QOD-NS total	4.4 [±6.9]	5.8 [±5.5]	1.4 [±1.4]	-4.2 – 1.5	5.6 [±6.7]	1.1 [±1.4]	-3.9 – 1.7

CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyposis; CRSsNP, chronic rhinosinusitis without nasal polyposis; SD, standard deviation; N, sample size; SNOT-22, 22-item Sinonasal Outcome Test survey; QOD-NS, Questionnaire of Olfactory Dysfunction-negative statements, OCES, olfactory cleft endoscopy score; LKES, Lund-Kennedy endoscopy score; CI, confidence interval; Δ postoperative change; SE, standard error. None of the statistical comparisons between controls and either CRS group were significant for any of the postoperative measures (p>0.050).

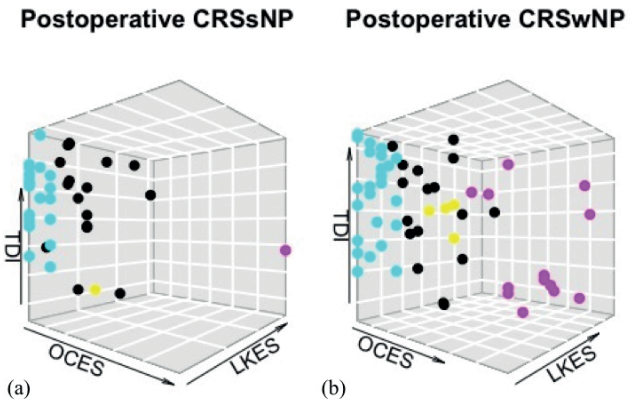

Figure 3. Three dimensional scatterplots of postoperative OCES, LKES, and TDI for CRSsNP (a) and CRSwNP (b). Points are colored corresponding to the following categories: Group 1 (normal OCES, normal LKES) = Cyan, Group 2 (normal OCES, severe LKES) = Yellow, Group 3 (severe OCES, severe LKES) = Magenta, Group 4 (severe OCES, normal LKES) = Green. Black represents subjects that did not fall into any group category. No subjects were classified into Group 4 for either CRSwNP or CRSsNP who had available postoperative TDI testing. Group 1 subjects (near perfect endoscopic scores) still showed highly variable degrees of OD, suggesting etiologies other than local inflammation may be at play.

have persistent hyposmia (mean Sniffin' Sticks total score: 27.6) despite endoscopic control of both sinuses and OC. As seen in Table 7, olfactory metrics in CRSwNP patients with near perfect endoscopy are not significantly different from control subjects.

Discussion

A comprehensive understanding of CRS outcomes requires a spectrum of instruments to assess local, regional and systemic factors. The OCES is a recently developed instrument designed to measure OC-specific factors visible on endoscopy. In a single institution study, it demonstrated high inter- and intra-rater reliability[3], as well as face and convergent validity. The current study added larger numbers of patients from multiple institutions in order to further examine convergent validity and responsiveness to change. Convergent validity tests constructs that are likely to be related. The key measures of olfaction for convergent validity are arguably psychophysical and psychosocial testing using Sniffin Sticks (or other olfactory tests) and QOD. In this regard, the OCES performed well with significant correlations across our population for Sniffin' Sticks total scores (R=-0.533, p<0.001) and QOD scores (R=0.388, p<0.001). Yet another aspect of convergent validity would be an ability to differentiate among groups with variable degrees of inflammation in the OC. As previously reported, the OCES does differ between CRS groups based upon polyp status[3]. This is not surprising, given that polyp grade is part of the OCES. However, the current study carries a step further and shows that OCES also differs between control patients and CRSsNP patients – two groups that do not have polyps. Discriminant validity assesses the ability to discriminate between variables that should not be related. Poletti used the OCES to examine a large group of OD patients from varying etiologies[5]. Similar to our results, the OCES did correlate with olfactory function in CRS subjects and differed from controls. They also nicely demonstrated discriminant va-

lidity, as OCES scores in subjects with idiopathic, post-viral and post-traumatic OD were similar to normosmic controls. This lack of correlation is expected given the fact that OD due to these non-sinonasal etiologies is not thought to occur secondary to localized mucosal conditions. Another aspect of instrument validation is response to change, which had not been previously studied. We were able to show that after surgery, OCES scores improved in both patients with CRSwNP and CRSsNP.

Otolaryngologists are familiar with sinus endoscopy and the LKES system. While it provides valuable information regarding control of sinus inflammation, this grading system does not assess the OC. In general, we found that the OCES and LKES provide complimentary information. For example, in the CRSwNP patients, OCES appears to provide stronger correlations with olfactory measures postoperatively and it may help to identify patients with persistent OC inflammation who would benefit from additional therapies targeting inflammation at this site. Meanwhile, the LKES appears to provide stronger correlations preoperatively. In CRSsNP there is less overall utility with either endoscopy scoring system. As our classifications of CRS become more refined and extend beyond simple presence or absence of nasal polyps, our metrics should similarly become more refined and precise. It is anticipated that metrics, such as the OCES, can be used in the future to understand subtle abnormalities, such as edema or mucus, and their precise anatomic localization. Other aspects of OCES, such as scarring or crusting that rarely occur in the OC may have impacted its utility.

We then considered OCES as a tool to help us understand and better treat persistent OD postoperatively. While there is certainly a continuum of endoscopic grading severity in both the OCES and LKES, for simplicity, patients could be broken down into 4 broad groups based upon the presence or absence of inflammation in the OC and sinuses. This is shown graphically in Figure 3. The first group would have near normal OCES and LKES, thus inflammation at both sites would be considered under good control. It appears that nearly 63% of CRSsNP and 39% of CRSwNP patients fall into this category. Interestingly, both CRSsNP and CRSwNP patients have similar mean Sniffin' Sticks scores with mild hyposmia (28.5 and 27.5, respectively). Once OCES and LKES are normal, olfactory metrics are indistinguishable from control subjects. This is despite the fact that our control subjects contained a larger proportion of females who typically have better olfaction. We posit that OD in these patients may be due to non-CRS causes such as DM, hypertension, or aging that could impact both control and CRS subjects. The CRS subjects could also suffer from permanent neural injury/atrophy related to CRS or past surgeries that are not readily detectable endoscopically. This has significant clinical implications, as further treatments targeting CRS or nasal inflammation are unlikely to be beneficial. The second group also has near perfect OCES, but has severe LKES. As seen in Tables 5 and 6, when OCES is near perfect, mean Sniffin' Sticks total scores slowly decrease as LKES worsens and this occurs regardless of polyp status. Mechanisms as to how this adjacent sinus inflammation can potentially impact olfaction may include altered airflow, nasal mucus composition or local microenvironment elements that are not detectable endoscopically. This has been suggested in CRS subjects, as OCES correlates with subjective sensation of airflow[5]. It would also be interesting in this group to determine if olfaction improves as sinus inflammation improves. The third group to consider would be patients with severely abnormal OCES and LKES. Nearly a quarter of CRSwNP patients fall into this category postoperatively, while it is relatively uncommon in CRSsNP patients. This group unfortunately suffers a "double hit" and experiences the worst olfaction with a mean Sniffin' Sticks total score near the anosmic range (18.0). OCES is useful in distinguishing this group from the second group above. Both have severe sinus inflammation but when the inflammatory process also involves the OC, olfaction seems to be more severely impaired. The fourth group has isolated severe OC inflammation despite near perfect LKES. Clinically, this may occur in patients with central compartment atopic disease, a recently described entity that preferentially affects the olfactory cleft and middle turbinates with relative sparing of the paranasal sinuses[12]. We did not see significant numbers of these patients in our study, at least postoperatively. Finally, surgeons must remember that most patients likely present with multi-factorial OD and it is not one single factor, but rather a combination of factors contributing to their clinical presentation.

Strengths of this study include its prospective, multi-institutional design with relatively large numbers of patients. One potential weakness in any study requiring postoperative follow up is patients that are lost. In this study, approximately 25% of patients operated upon, were either lost to follow up or did not have complete data at 6 month follow up and this could potentially impact findings. Areas for further study include the relationship between OCES and other olfactory-specific metrics to include OC imaging, local cytokine/protein production and histologic assessments and its potential utility in further refining our classification of CRS and its impact upon olfaction. Given that this study was conducted in tertiary rhinology practices, the applicability to general otolaryngology practices is unknown. While one strength of this study was inclusion of a control group, it is still important to understand we were unable to control for all variables that impact olfaction, including sex and years of education[13-15].

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Conclusion

In conclusion, this study further validates the OCES as an instru-

ment to evaluate and provide insight into mechanisms of OD that occur in CRS patients. Future studies are needed to determine its precise utility in this challenging group of patients.

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Authorship contribution

All authors contributed to the design and execution of the study, enrolling patients, review and editing of manuscript and interpretation of data.

Conflict of interest

RJS: Consultant for Healthy Humming, Optinose, Stryker, GSK; DMB: Consultant for Medtronic, ZMS: Consultant for Healthy Humming, Optinose.

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