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ORIGINAL ARTICLE

Clinical outcomes of Eustachian tube dysfunction in chronic rhinosinusitis following endoscopic sinus surgery

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Abstract

Background: The effects of endoscopic sinus surgery (ESS) on the symptom burden of Eustachian tube dysfunction (ETD) in chronic rhinosinusitis (CRS) patients were investigated.

Methods: Ninety-two patients with CRS following ESS were prospectively enrolled and followed up every 3 months for 1 year. The 7-item ETD Questionnaire (ETDQ-7) and 22-item Sino-Nasal Outcome Test (SNOT-22) were administered before ESS and at each visit following ESS.

Results: Before surgery, 25% of patients reported ETDQ-7 scores ≥ 14.5, indicating the presence of ETD. The mean preoperative ETDQ-7 and SNOT-22 scores were 13.3 and 40.0, respectively. The mean ETDQ-7 and SNOT-22 scores were significantly decreased to 8.2 and 17.0 at 1 year following ESS, respectively. Most patients reported alleviation of their symptoms within the first 3 months, and the prevalence of ETD had decreased to 3.3% at 1 year. Patients who received revision surgery had higher ETDQ-7 scores during the follow-up period. Additionally, 5.4% of patients reported worsening of their symptoms.

Conclusion: ETD symptoms can be effectively alleviated in most patients within 3 months following ESS. However, 5.4% of patients reported worsening of their symptoms at the 1-year follow-up. Additional objective studies should be conducted to evaluate Eustachian tube function thoroughly in CRS patients.

Keywords: ETDQ-7; Middle ear; Otologic symptom; Revision sinus surgery; SNOT-22

1. INTRODUCTION

The Eustachian tube has several unique functions, including pressure equalization, mucociliary clearance, and auditory protection of the middle ear.[1] Impaired dilatory function or patency of the tube, referred to as Eustachian tube dysfunction (ETD), causes otologic symptoms such as aural fullness, otalgia, a sensation of pressure, or muffled hearing.[2] Of the various pathogeneses that may cause ETD, sinonasal diseases are important comorbidities.[3,4] The prevalence of ETD in patients treated for various sinonasal diseases at a tertiary rhinology clinic was 43.3%, and there was a positive correlation between ETD and rhinologic symptoms.[5]

In chronic rhinosinusitis (CRS), inflammatory mucus can be deposited in the Eustachian tube orifice, leading to obstruction. Moreover, the inflammation and mucosal edema may extend to the nasopharyngeal region and contribute to ETD.[6] Furthermore, nearly half of CRS patients have been found to have ETD.[7] Since CRS is highly associated with ETD, treatment of CRS may decrease inflammatory burden, restore normal tube function, and improve related otologic symptoms. Despite this, few studies have investigated the otologic outcomes of CRS patients after endoscopic sinus surgery (ESS). Previous studies using the otologic subdomain of the 22-item Sino-Nasal Outcome Test (SNOT-22) to evaluate ETD symptoms after ESS found significant improvement in symptom scores.[8,9] However, these surveys used questionnaires that were not validated specifically for ETD-associated symptoms.

In this study, we used the 7-item ETD Questionnaire (ETDQ-7), a validated tool for quantitative evaluation of ETD, to assess changes of ETD symptoms following ESS.[2] The purpose of this study was to determine the prevalence and clinical outcomes of ETD-associated symptoms in CRS patients following ESS.

2. METHODS

2.1. Study population

This study included CRS patients with and without nasal polyps treated between December 2016 and November 2017 at Chang Gung Memorial Hospital, Kaohsiung, Taiwan. The patients were diagnosed according to the clinical practice guidelines of EPOS (2012).[10] All patients underwent medical treatment, including intranasal corticosteroid sprays, for at least 2 months with or

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without oral steroids/oral antibiotics for 2 weeks. Patients with an unsatisfactory response to medical treatment who consented to surgical intervention were candidates for this study. Those with a previous history of radiotherapy of the head or neck region, ear surgery, or pharyngeal surgery were excluded. After ESS, all patients underwent standard postoperative therapeutic protocols, including daily saline nasal irrigation and medical therapy, when necessary.[10]

All eligible patients provided written informed consent. Sinonasal endoscopy, otoscopy, and computed tomography (CT) were performed before ESS. The endoscopic findings and CT images were scored using the modified Lund-Kennedy and Lund-Mackay scoring systems, respectively.[11,12] The levels of total immunoglobulin E (IgE) and allergen-specific IgE were measured to identify allergic rhinitis candidates. All patients completed the SNOT-22 and ETDQ-7 before and after the operation. The rhinologic subdomain included SNOT-22 items 1-6, 21, and 22. The otologic subdomain was defined as SNOT-22 items 7-9 (ear fullness, dizziness, and ear pain). The ETDQ-7 consists of seven questions, with a total score ranging from 7 to 49; a score ≥ 14.5 is indicative of ETD.[2] All patients were followed up and completed survey evaluations postoperatively at 3-month intervals for up to 1 year after ESS. Patients lost to regular follow-up visits were excluded from this study. The study protocol was approved by the medical ethics and human clinical trial committees of Chang Gung Memorial Hospital (Refs. 202101772B0, 105-3651C, and 106-0270C).

2.2. Statistical analysis

A two-sided Spearman rank correlation test was used to explore associations among ETDQ-7 and SNOT-22 scores. The comparisons of preoperative and postoperative ETDQ-7 scores between various patient characteristics were statistically analyzed using the Wilcoxon signed rank test. The changes among different ETDQ-7 subgroups before and after ESS were statistically analyzed using the McNemar-Bowker test (Fig. 1). A p-value < 0.05 was considered to indicate statistical significance. All analyses were performed using SPSS version 22 software (IBM Corp., Armonk, NY, USA).

3. RESULTS

3.1. Patient characteristics

From the initial 120 consecutive CRS patients evaluated, 28 patients were excluded due to history of pharyngeal or ear surgeries (three), history of radiotherapy in head and neck region (two), and incomplete follow-up intervals (23). Finally, 92 CRS patients were prospectively enrolled and completed all follow-up evaluations at 3-month intervals during the 1-year study period. The mean ± SD age of the enrolled patients was 46.4 ± 15.7 years old, and 67.4% were women. The preoperative ETDQ-7 and SNOT-22 scores of the entire cohort were 13.3 ± 8.3 and 40.0 ± 20.9, respectively. The preoperative modified Lund-Kennedy and Lund-Mackay scores were 4.5 ± 2.9 and 9.2 ± 6.3, respectively. The detailed demographic data of the study group are summarized in Table 1.

3.2. Preoperative ETDQ-7 score

There was no significant difference in preoperative ETDQ-7 scores between the different clinical characteristics, but a higher average ETDQ-7 score was found for revision cases at 1 year following ESS (Table 2). The preoperative SNOT-22 and ETDQ-7 scores were weakly correlated ($\gamma = 0.397$; $p < 0.001$) with clinical significance. The preoperative ETDQ-7 score was weakly correlated ($\gamma = 0.265$; $p = 0.011$) with the SNOT-22 rhinologic subdomain and was moderately correlated ($\gamma = 0.572$; $p < 0.001$) with the SNOT-22 otologic subdomain. The preoperative ETDQ-7 score was not correlated with disease severity as evaluated by the Lund-Mackay CT score and modified Lund-Kennedy endoscopy score.

3.3. Prevalence of ETD before and after ESS

ETDQ-7 scores ≥ 14.5 were suggestive of ETD, which is consistent with the formal criteria of ETD.[2] We further divided the patients who did not meet ETD criteria into two subgroups containing those without otologic symptoms (ETDQ-7 = 7) and those with some otologic symptoms (7 < ETDQ-7 < 14.5). Preoperatively, 30 patients (32.6%) reported no otologic symptoms, 39 patients (42.4%) reported some otologic symptoms, and 23 patients (25%) were diagnosed with ETD. At 3 months after ESS, the percentage of patients without otologic symptoms had significantly increased from 32.6% to 76.1%, and the percentage of ETD had significantly decreased from 25% to 5.4% ($p < 0.001$). The percentage of patients with ETD had further decreased to 3.3% at 1 year. However, the percentages of patients with some otologic symptoms were slightly higher at 9 months (21.7%) and 1 year (23.9%) than at 6 months (15.2%) after ESS without statistical significance (Fig. 1).

3.4. Changes in ETDQ-7 scores after ESS

The changes in ETDQ-7 scores for the entire cohort following ESS are shown in Fig. 2. Most patients' ETDQ-7 scores decreased significantly within the first 3 months. We defined a change in ETDQ-7 (change ≥ 5) more than 10% of the maximal ETDQ-7 score, as indicating symptom improvement or deterioration. At 1 year after ESS, 34 patients (37%) reported improvement, 53 (57.6%) patients reported stable symptoms, and five patients (5.4%) reported worsening of their ETD symptoms. Additionally, the mean ETDQ-7 and SNOT-22 scores decreased significantly to 8.2 and 17.0, respectively ($p < 0.001$ for all). The postoperative 1-year ETDQ-7 scores for various clinical characteristics are shown in Table 2. No significant difference was found, except that revision cases had higher ETDQ-7 scores. Patients who underwent revision surgery had significantly higher postoperative ETDQ-7 scores at all follow-up intervals compared with patients who underwent primary surgery ($p < 0.05$ for all). Postoperative SNOT-22 scores were also significantly higher for revision cases within 6 months after ESS, but after 6 months, the scores showed no significant difference (Table 3). Logistic regression analysis was performed to evaluate the independent predictors of persistent otologic symptoms (ETDQ-7 scores > 7) following ESS. The univariate [odds ratio (OR), 4.822; 95% CI, 1.365-17.033; $p = 0.015$] and multivariate analyses (OR, 5.328; 95% CI, 1.273-22.297; $p = 0.022$) showed revision surgery was an independent predictor of persistent otologic symptom 1-year postoperatively (Table 4).

3.5. Changes in ETDQ-7 scores in preoperative ETD group

There were 23 patients who reported ETD before ESS. The mean preoperative, postoperative 3-month, 6-month, 9-month, and 1-year ETDQ-7 score was 25.2, 10.6, 8.4, 8.0, and 7.7, respectively. The ETDQ-7 score was significantly decreased from preoperative to postoperative 3 month ($p < 0.001$) and from postoperative 3 month to postoperative 6 month ($p = 0.028$). One-year post-ESS, 18 patients (78.3%) reported no otologic symptoms, five patients (21.7%) reported some otologic symptoms, and no patients reported ETD.

4. DISCUSSION

ETD is common in patients with sinonasal disease, including allergic rhinitis, nasal septum deviation, inferior turbinate

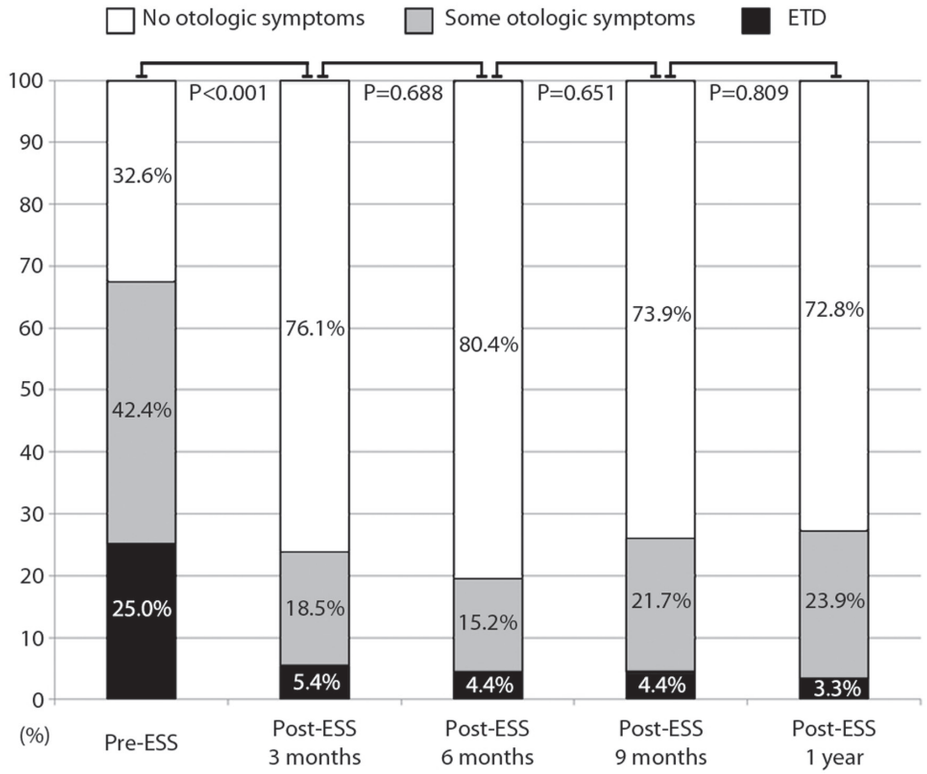

Fig. 1 Distribution of ETD symptom subgroups before and after ESS. ESS = endoscopic sinus surgery; ETD = Eustachian tube dysfunction

Table 1

Patient demographic data

Patient characteristics	Mean ± SD	n (%)
Age (y)	46.4 ± 15.7	
Female		62 (67.4)
Male		30 (32.6)
CRSwNP		39 (42.4)
Allergic rhinitis		30 (32.6)
Asthma		5 (5.4)
Tobacco use		13 (14.1)
Prior sinus surgery		12 (13)
Septal deviation		37 (40.2)
SNOT-22 score	40.0 ± 20.9	
ETDQ-7 score	13.3 ± 8.3	
Lund-Mackay CT scores	9.2 ± 6.3	
Modified Lund-Kennedy endoscopy scores	4.5 ± 2.9	

CRSwNP = chronic rhinosinusitis with nasal polyps; CT = computed tomography; ETDQ-7 = 7-Item Eustachian Tube Dysfunction Questionnaire; SNOT-22 = 22-Item Sino-Nasal Outcome Test.

hypertrophy, and CRS.[6,9,13–15] Marino et al[5] found a 43.3% prevalence of significant ETD symptoms in patients visiting a tertiary rhinology clinic for the treatment of rhinologic problems. Previous studies have found that in cases of CRS, the prevalence of otologic symptoms is 15%-61%.[6,9] Tangbumrungtham et al[7] initially evaluated ETD symptoms in CRS patients using the ETDQ-7 and found a 48.5% prevalence rate. In our cohort, one-quarter of the CRS patients had clinically significant ETD symptoms, which was lower than in previous results. ETDQ-7 scores showed a significant correlation with SNOT-22 scores

Table 2

Comparison of preoperative and postoperative 1-y ETDQ-7 scores

	Pre-ESS ETDQ-7		Post-ESS ETDQ-7	
Patient characteristics	**Median (IQR)**	***p***	**Median (IQR)**	***p***
Age (y)				
≥50 y/o (n = 45)	10.0 (7.0-13.0)	0.226	7.0 (7.0-9.0)	0.087
<50 y/o (n = 47)	10.0 (7.0-18.0)		7.0 (7.0-7.0)	
Sex				
Male (n = 30)	11.5 (7.0-19.5)	0.291	7.0 (7.0-7.0)	0.189
Female (n = 62)	9.5 (7.0-13.3)		7.0 (7.0-9.0)	
Type of rhinosinusitis				
CRSsNP (n = 53)	10.0 (7.0-13.0)	0.484	7.0 (7.0-9.0)	0.299
CRSwNP (n = 39)	11.0 (7.0-18.0)		7.0 (7.0-7.0)	
Allergic rhinitis				
Yes (n = 30)	10.5 (7.0-16.3)	0.757	7.0 (7.0-8.0)	0.920
No (n = 62)	10.0 (7.0-14.3)		7.0 (7.0-8.0)	
Asthma				
Yes (n = 5)	13.0 (10.5-22.0)	0.325	7.0 (7.0-11.0)	0.428
No (n = 87)	10.0 (7.0-15.0)		7.0 (7.0-8.0)	
Tobacco use				
Yes (n = 13)	12.0 (7.0-20.0)	0.434	7.0 (7.0-9.0)	0.070
No (n = 79)	10.0 (7.0-14.0)		7.0 (7.0-7.0)	
Prior sinus surgery				
Primary surgery (n = 80)	10.0 (7.0-14.0)	0.859	7.0 (7.0-7.0)	0.004[a]
Revision surgery (n = 12)	10.0 (7.0-26.3)		9.5 (7.0-11.5)	

CRSsNP = chronic rhinosinusitis without nasal polyps; CRSwNP = Chronic rhinosinusitis with nasal polyps; ESS = endoscopic sinus surgery; ETDQ-7 = 7-Item Eustachian Tube Dysfunction Questionnaire; IQR = interquartile range (Q25-Q75).
[a]Statistical significance.

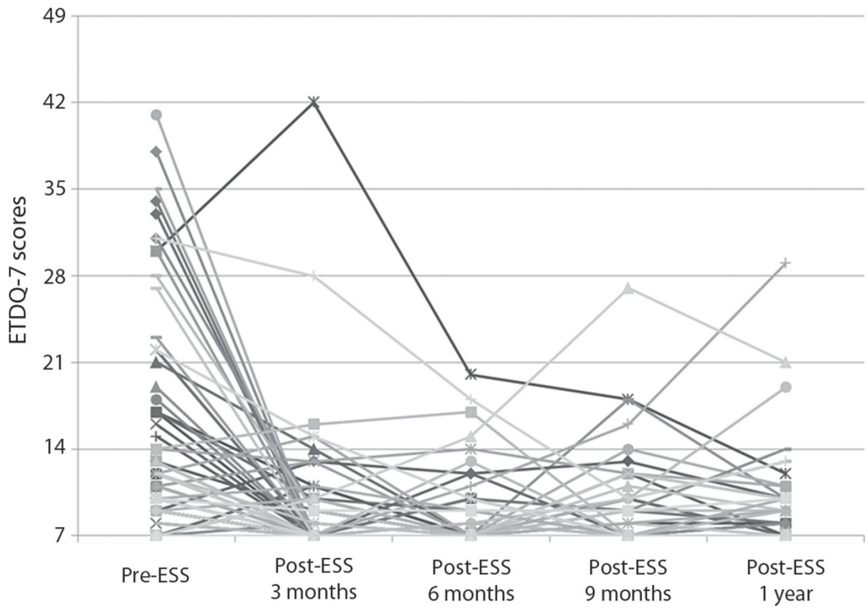

Fig. 2 The change in ETDQ-7 scores for the entire cohort following ESS. ESS = endoscopic sinus surgery; ETDQ-7 = 7-item Eustachian Tube Dysfunction Questionnaire

but no correlation with disease severity as evaluated by the Lund-Mackay and modified Lund-Kennedy scores. Similar results were reported by Tangbumrungtham et al.[7] Previous studies found a higher preoperative ETDQ-7 score in CRS with nasal polyps patients.[16,17] However, the preoperative ETDQ-7 scores showed no significant difference among CRS patients with and without polyps patients in our study. These results may reflect a lower inflammatory burden in our study population. Compared with Western population, a lower prevalence of CRS comorbid with asthma was found in Eastern Asian population.[18] Otherwise, the CRS with nasal polyps patients was less related to eosinophilic disease in Eastern Asian population.[19] Therefore, our results may not be compatible with other populations.

Since a link exists between sinonasal disease and the middle ear, treatment of sinonasal disease may help to improve otologic symptoms.[5,20,21] In CRS patients, a favorable outcome for otologic symptoms was reported following ESS in previous reports. A retrospective study by Stoikes et al[6] found great improvement in ear fullness (84.3%) and ear pain (84%) with a mean 14-month follow-up period. Maniakas et al[9] also found a favorable change in the ear domain (approximately 75%) using SNOT-22. Teo et al[8] reported 61% and 43% improvements in ear fullness and ear pain, respectively. Consistent with the results of Teo et al,[8] in the present study, ETD improved in 37% (34/92) of patients after ESS. In the studies of Stoikes et al[6] and Maniakas et al,[9] patients without preoperative otologic problems were excluded. This may have resulted in underestimating the number of patients who reported worse symptoms and would contribute to estimates implying a greater improvement after ESS. Higgins et al[22] found a poor outcome in patients with temporomandibular joint dysfunction and higher preoperative ETDQ-7 scores. In our study, a relatively poor outcome in ETD symptoms was found for revision cases following revised ESS. This finding was not fully explained by increased sinonasal symptoms in revision cases following ESS. In revision patients, the average SNOT-22 score was similar to that in patients who underwent primary surgery in the last 1-year survey, although the rate of decline was slower (Table 3). We hypothesize that a longer period of inflammation affecting the nasal cavity and middle-ear region may lead to increased symptoms of ETD in revision cases. A summary of related studies is located in Table 5.

To assess the response of ETD in CRS patients following ESS, we followed them up at 3-month intervals for up to 1 year. Most patients reported dramatic improvement in their ETD symptoms in the first 3 months (Fig. 2), and the largest percentage of patients reported no otologic problems in the 6 months

Table 3

The difference in ETDQ-7 and SNOT-22 scores between primary and revision patients for pre-ESS and follow-up intervals

		Pre-ESS	3 mo	6 mo	9 mo	1 y
		Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
ETDQ-7	Primary surgery	10.0 (7.0-14.0)	7.0 (7.0-7.0)	7.0 (7.0-7.0)	7.0 (7.0-7.0)	7.0 (7.0-7.0)
	Revision surgery	10.0 (7.0-26.3)	8.0 (7.0-13.3)	7.0 (7.0-9.0)	8.5 (7.0-10.0)	9.5 (7.0-11.5)
	p	0.859	0.016[a]	0.042[a]	0.009[a]	0.004[a]
SNOT-22	Primary surgery	36.5 (22.0-54.0)	13.5 (7.3-26.8)	13.5 (8.0-24.5)	16.0 (6.0-33.0)	14.0 (5.3-24.8)
	Revision surgery	46.5 (26.0-59.8)	33.0 (22.3-41.8)	27.5 (16.0-47.8)	24.5 (15.3-33.5)	14.5 (8.5-18.8)
	p	0.719	0.004[a]	0.014[a]	0.258	0.723

ESS = endoscopic sinus surgery; ETDQ-7 = 7-Item Eustachian Tube Dysfunction Questionnaire; IQR = interquartile range (Q25-Q75); SNOT-22 = 22-Item Sino-Nasal Outcome Test.
[a]Statistical significance.

Table 4

Logistic regression analysis of factors associated with poor outcome of Eustachian tube function 1-y following ESS

	Univariate analysis			Multivariate analysis		
Patient characteristics	**OR**	**95% CI**	***p***	**OR**	**CI**	***p***
Age (y)						
<50 y/o (n = 47)		1			1	
≥50 y/o (n = 45)	2.330	0.902-6.017	0.810	2.531	0.872-7.349	0.088
Sex						
Female (n = 62)		1			1	
Male (n = 30)	0.566	0.199-1.609	0.285	0.838	0.264-2.653	0.763
Type of rhinosinusitis						
CRSsNP (n = 53)		1			1	
CRSwNP (n = 39)	0.546	0.208-1.439	0.221	0.757	0.240-2.383	0.634
Allergic rhinitis						
No (n = 62)		1		1		
Yes (n = 30)	0.963	0.360-2.572	0.939	1.480	0.463-4.733	0.509
Asthma						
No (n = 87)		1			1	
Yes (n = 5)	1.855	0.291-11.816	0.513	2.927	0.312-27.498	0.347
Tobacco use						
No (n = 79)		1			1	
Yes (n = 13)	0.191	0.023-1.533	0.122	0.141	0.014-1.433	0.098
Prior sinus surgery						
Primary surgery (n = 80)		1			1	
Revision surgery (n = 12)	4.822	1.365-17.033	0.015[a]	5.328	1.273-22.297	0.022[a]

CRSsNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyps; ESS = endoscopic sinus surgery; OR = odds ratio.
[a]Statistical significance.

following ESS. However, the percentage of patients who reported some otologic symptoms tended to increase after that time point (Fig. 1). It should be noted that some patients reported symptom deterioration after ESS. Previous studies reported deterioration of otologic symptoms in 2.9%-12% of patients.[6,8,9] In this cohort, we found that 5.4% (5/92) of patients reported worse ETD symptoms compared with their preoperative status, perhaps due to chronic sinonasal inflammation. In this study, at 1

Table 5

The summary of studies in investigation of Eustachian tube function following ESS

Study	**No.**	**Study design**	**Follow-up period**	**Nasal polyps**	**Survey tools**	**Results**
Stoikes and Dutton[6]	168	Retrospective	Mean 14 mo	8.9%	Self-designed questionnaire	Significant improvement of ear fullness/congestion, ear cracking/popping, dizziness, and ear pain after sinus surgery.
Teo et al[8]	395	Prospective	Mean 13.9 mo	37.7%	SNOT-22 Otologic domain	Significant improvement of otologic symptom scores, included ear fullness, dizziness and ear pain.
Maniakas et al[9]	131	Prospective	Mean 3.8 mo	No report	SNOT-22 Otologic domain	A total of 78.8% patients reported an improvement of ear fullness score, 73.3% patients reported an improvement of ear painscore.
Chang et al[16]	302	Retrospective	6 mo	41.7%	ETDQ-7	On multivariate analysis, ETD improvement was associated with higher preoperative ETDQ-7 score, higher preoperative SNOT-22 score, higher preoperative SNOT-22 ear subscore, posterior ethmoidectomy, and postoperative corticosteroid spray use.
Bowles et al[17]	57	Prospective	9 mo	40.4%	ETDQ-7 Tympanogram	Mean ETDQ-7 scores were significantly lower following ESS. Type A tympanograms increased form 76.6% preoperatively to 96% postoperatively.
Higgins et al[22]	60	Prospective	2 mo	30.0%	ETDQ-7	ESS was associated with ETDQ-7 improvement. Nasal polyposis was associated with a higher probability of ETDQ-7 normalization. Factors associated with failure of ETDQ-7 normalization included TMJD and high preoperative ETDQ-7.
Choi et al[23]	60[a]	Prospective	3 mo	73.3%	ETDQ-7 Valsalva test Inflation test Deflation test	Compared with the group without sinusitis, the ESS group showed significant improvement of E-tube function after surgery in the ETDQ-7, right Valsalva test, right deflation test, and left deflation test.
Chen et al[24]	70	Prospective	2-3 mo	72.9%	ETDQ-7 Tympanogram	Failure of normalization of ETDQ-7 postoperatively was associated with allergic rhinitis and higher preoperative SNOT-22 score in multivariate analysis. Preoperative type B tympanogram changed to type A or type C in 58.3% postoperatively.
Chen et al (this study)	92	Prospective	12 mo	42.4%	ETDQ-7	Patients who received revision surgery had higher ETDQ-7 scores during the follow-up period. The multivariate analysis showed revision surgery was an independent predictor of persistent otologic symptom 1-y postoperatively.

ESS = Endoscopic sinus surgery; ETDQ-7 = 7-Item Eustachian Tube Dysfunction Questionnaire; SNOT-22 = 22-Item Sino-Nasal Outcome Test; TMJD = temporomandibular joint dysfunction.
[a]ESS (n = 30) vs other nasal surgeries (n = 30).

year following ESS, SNOT-22 scores were significantly higher in patients with worse symptoms (mean [median] = 27.6 [30.0] vs 16.4 [13.0]; p = 0.023) compared with those with stable or improved ETD symptoms. Additionally, one patient reported worse ETD symptoms due to postoperative nasal saline irrigation. Adverse effects due to nasal saline irrigation are not uncommon because otologic adverse events usually improve after stopping irrigation and medication treatment.[25,26]

Although this prospective study demonstrated the 1-year outcomes of ETD in CRS patients following ESS, additional detailed objective studies of ETD should be performed. Choi et al[23] found significant improvement in Eustachian tube function after ESS in the right Valsalva test, right deflation test, and left deflation test. Bowles et al[17] and Chen et al[24] found type A tympanograms were increased postoperatively. Currently, ETD is diagnosed clinically using otologic tests such as the tympanogram, inflation/deflation test, sonotubometry, and tubomanometry; however, there is no universally accepted gold standard test for ETD.[27,28] Future studies should objectively evaluate the possible pathological mechanisms of ETD in CRS patients.

ESS effectively reduced ETD symptoms, with most CRS patients reporting alleviation of these symptoms within the first 3 months after the operation. However, patients undergoing revision ESS had relatively poor results regarding ETD symptoms for the entire follow-up period. After 1 year, 5.4% of patients suffered from increased symptoms, so medical professionals should be aware of potentially negative results. Additional objective studies should be conducted to characterize further the relationship between ETD and CRS and to identify the ideal treatment option for patients with persistent ETD symptoms.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A148.

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