Current Eye Research

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/icey20

Association of Dry Eye with Laryngopharyngeal Reflux in Clinical Practice

S. Bonini, M. Labetoulle, E. Messmer, P. Aragona, J. M. Benitez Castillo, G. Ciprandi, V. Damiani, M. Irkec, C. Baudouin & M. Rolando

To cite this article: S. Bonini, M. Labetoulle, E. Messmer, P. Aragona, J. M. Benitez Castillo, G. Ciprandi, V. Damiani, M. Irkec, C. Baudouin & M. Rolando (2022) Association of Dry Eye with Laryngopharyngeal Reflux in Clinical Practice, Current Eye Research, 47:2, 214-219, DOI: 10.1080/02713683.2021.1971721

To link to this article: https://doi.org/10.1080/02713683.2021.1971721

Published online: 19 Sep 2021.

CURRENT EYE RESEARCH
2022, VOL. 47, NO. 2, 214–219
https://doi.org/10.1080/02713683.2021.1971721

Taylor & Francis
Taylor & Francis Group

Association of Dry Eye with Laryngopharyngeal Reflux in Clinical Practice

S. Bonini[a*], M. Labetoulle[b*], E. Messmer[c*], P. Aragona[d], J. M. Benitez Castillo[e], G. Ciprandi[f], V. Damiani[g], M. Irkec[h], C. Baudouin[i], and M. Rolando[j]

[a]Ophthalmology Department, Campus Bio-Medico University, Rome, Italy; [b]Ophthalmology Département, Hôpitaux Universitaires Paris-Sud, APHP, Université Paris-Saclay, IDMIT Infrastructure, CEA, Inserm U1184, Fontenay-aux-Roses Cedex, France; [c]Department of Ophthalmology, Ludwig-Maximilians-University, Munich, Germany; [d]Department of Biomedical Sciences, Ophthalmology Clinic, University of Messina, Messina, Italy; [e]Departamento de Oftalmología, Hospital Clínico San Carlos, Clínica Rementeria, Instituto Investigaciones Oftalmologicas Ramon Castroviejo, Universidad Complutense, Madrid, Spain; [f]Allergy Clinic, Casa di Cura Villa Montallegro, Genoa, Italy; [g]DMG Italia Medical Department, Rome, Italy; [h]Department of Ophthalmology, Faculty of Medicine, Hacettepe University, Ankara, Turkey; [i]Quinze-Vingts National Eye Hospital, IHU ForeSight, Paris Saclay University, Paris, France; [j]Ocular Surface Centre, ISPRE Ophthalmics, Genoa, Italy

ABSTRACT

Background: Dry eye disease (DED) is a common disorder, accounting for up to 35% of the general population. Therefore, we hypothesized that laryngopharyngeal reflux (LPR), inducing refluxate rising into airways, may involve the ocular surface and may either induce or worsen DED.

Aim: To investigate the prevalence and relevance of suspected LPR in DED patients and subjects with refractive problems (RP) without DED, they were defined as non-dry eye group (NEG) in clinical practice.

Methods: This retrospective study included consecutive patients evaluated because of dry eye-like symptoms at eight tertiary ophthalmological clinics. Parameters included reflux symptom index (RSI), ocular surface disease index (OSDI), symptom assessment in dry eye (SANDE) for frequency and severity, Schirmer test, tear break-up time (BUT), and Oxford grading.

Results: The study included 245 subjects (72.5% females; mean age 56.3 years), 152 DED patients, and 93 sex- and age-matched NEG subjects. Pathological RSI (score>13) was detected in 80 subjects (32.6%); 68 (85%) with DED and 12 (15%) CG (OR = 8; $p < .0001$). In NEG, pathological RSI was associated with higher SANDE (Frequency and Severity), OSDI, and Schirmer scores (OR = 16.36; 14.51; 12.54; and 7.22, respectively. In DED patients, pathological RSI was associated with higher OSDI values (OR = 8.75).

Conclusion: Patients with DED are at eight times higher risk for having pathological RSI than NEG patients. Moreover, pathological RSI was associated with more severe ocular symptoms both in DED and non-DED patients. The role of LPR in definite DED patients remains to be clarified, but this condition deserves to be investigated in managing patients with DED symptoms.

ARTICLE HISTORY
Received 19 April 2021
Revised 24 June 2021
Accepted 13 August 2021

KEYWORDS
Dry eye disease; laryngopharyngeal reflux; RSI; ocular surface; symptom perception

Introduction

Dry eye disease (DED) is an ocular surface disorder affecting up to 35% of the general population worldwide.[1] The Tear Film and Ocular Surface Society (TFOS) Dry Eye Workshop (DEWS) II stated that "Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles".[2] Various pathogenic mechanisms are involved in DED, and some risk factors may worsen the clinical feature, including ocular surgery, electronic device use, contact lens wearing, and environmental factors as dry and cold air, pollution, smoke, and irritants.[3–7] In addition, toxic substances significantly contribute to DED, mainly concerning iatrogenic interventions (preservatives and systemic drugs), dysbiosis, and cosmetics.[8]

Previous observations allowed to imagine that some patients with ocular surface symptoms may frequently present complaints related to gastric reflux. Gastric reflux is a physiological phenomenon, but some subjects may lead to gastroesophageal reflux disease (GERD).

The typical GERD symptoms include heartburn and regurgitation. The severity of GERD symptoms depends on the esophageal damage caused by the exposure to gastric refluxate containing acid and pepsin. However, gastric reflux may overflow, flooding the airways, mainly the upper airways. As a result, GERD's extra-esophageal manifestations occur; the most common is laryngopharyngeal reflux (LPR).[9] LPR may be considered a new clinical entity based on newly discovered findings of the disease's specific pathogenesis.[10,11] As laryngeal and pharyngeal mucosa do not possess the oesophageal protective mechanisms, the stomach content's digestive activity quickly leads to respiratory mucosal lesions. Notably, laryngopharyngeal reflux occurs most commonly during

CONTACT G. Ciprandi gio.cip@libero.it Allergy Clinic, Casa di Cura Villa Montallegro, Via Boselli 5, Genoa 16146, Italy
*These authors contributed equally to this work.

the day due to the upper oesophageal sphincter dysfunction. This aspect is intriguing as typical GERD symptoms usually occur in the supine position and overnight. The Position Statement of the American Academy of otolaryngologists identified the most common symptoms of LPR, including hoarseness, *globus pharyngeus*, dysphagia, cough, chronic throat clearing, and sore throat.[12] LPR also represents a relevant burden concerning social and personal costs and impaired quality of life.[13]

From a pathophysiological perspective, low pH of refluxate and pepsin induce chronic mucosal inflammation.[14,15] Pepsin is a proteolytic enzyme deriving from pepsinogen and activated by low pH (at least <4) produced exclusively in the stomach. Therefore, pepsin detection outside the gastric area is a biomarker for gastric reflux.[16] Several studies investigated pepsin in different organs, including the larynx, pharynx, paranasal sinus, mouth, and internal ear, as recently summarized.[17] Consistently, pepsin was also documented in the tears of patients with gastro-oesophageal reflux disease[18] and children with LPR.[19]

Moreover, it has been reported that patients with ocular surface disease, characterized by inflammation, frequently (34%) presented LPR.[20] A very recent study evidenced pepsin-related ocular surface damage and dry eye in LPR patients.[21] However, apart from these limited reports, there is a gap in the literature concerning the real pathogenic role of LPR in DED patients. As a result, the current study tested the hypothesis that LPR could be associated with DED and worsen ocular symptoms. This idea could change the clinical approach in DED patients, as they could benefit from adequate LPR treatment, and practitioners should recognize the possible LPR comorbidity in patients with DED. Based on this background, the present retrospective multicenter study evaluated a group of DED patients and sex and age-matched patients with refractory problems (considered as non-dry eye group) recruited in daily ophthalmological clinical practices. This study aimed to investigate the frequency of suspected LPR and define a possible relationship between LPR and DED severity in clinical practice.

Materials and methods

Patients

The current cross-sectional retrospective study enrolled 245 consecutive outpatients (178 females and 67 males, mean age 56.33 ± 18.72 years) in 8 tertiary ophthalmological centers. The subjects were subdivided into two groups: patients with DED diagnosis (152) and 93 referrals for ocular problems, such as refractive problems, apart from DED, considered Non-dry Eye Group (NEG).

The study was conducted according to the tenets of the Declaration of Helsinki. Therefore, all patients signed informed consent concerning the medical procedures and privacy. In addition, the administration of questionnaires and execution of ophthalmological testing were routinely performed.

Inclusion criteria were DED diagnosis for the reference group. Exclusion criteria for the reference group were other ocular diseases apart from DED, including allergic, autoimmune, inflammatory, and infectious diseases, systemic disorders, including autoimmunity, cancer, and immunodeficiency, and medications, such as local and systemic anti-inflammatory and immunosuppressant drugs, that could interfere with the interpretation of results. The NEG's inclusion criteria were refractive problems; the exclusion criteria were the same and the DED diagnosis.

Parameters

Dry eye disease was diagnosed according to validated criteria.[2] Laryngopharyngeal reflux diagnosis was based on the questionnaire Reflux Symptom Index.

DED was assessed by taking the history, performing a complete eye examination, and using the symptom perception by SANDE, ocular surface symptom index (OSDI) questionnaire, Schirmer test, Break Up Time test, and eye surface staining scored by the Oxford grading scale. These tests are performed in daily practice.

Symptom perception was evaluated using the "Symptom Assessment iN Drye Eye" (SANDE) questionnaire utilizing a 100 mm horizontal VAS technique (0 = absence, 100 = maximum) to quantify the severity and frequency of ocular dryness and/or irritation.[22]

OSDI is a 12-item questionnaire specifically conceived to investigate ocular symptoms.[23] Further, its reliability and validity were documented by confirmatory studies.[24,25] Researchers and clinicians successfully used OSDI in patients with different eye diseases.[26] The OSDI scoring was performed according to a four-point scale: normal (≤ 12), mild,[13–22] moderate,[23–32] and severe (≥ 33), as previously reported.[27,28]

The standard tear break-up-time (BUT) measurement was performed by instilling a fluorescein drop into the inferior fornix.[29] The time-lapse between the last blink and the appearance of the first randomly distributed dark discontinuity in the fluorescein-stained tear film was measured three times, and the mean value of the measurements was calculated. Normal values should be > 10 seconds.[29]

Schirmer test was performed without topical anesthesia by placing a narrow filter paper strip (5 x 35 mm strip of Whatman #41 filter paper) in the inferior cul-de-sac. Normal values should be ≥ 5 mm/5 minutes.[30]

Staining of the ocular surface was assessed using the Oxford scale, consisting of a six-point (0 = normal; VI = severe) grading.[31] The reliability and repeatability of the Oxford scale were excellent.[32] Findings were separately reported for the right eye (Oxford-RE) and left eye (Oxford-LE).

Reflux Symptom Index (RSI) is a self-administered nine-item questionnaire developed by Belafsky to assess symptoms in patients with reflux disease.[33] Each item's scale ranges from 0 (no problem) to 5 (severe problems), with a maximum score of 45. It has been concluded that RSI has high reproducibility and validity for the diagnosis of reflux if an RSI score >13 is defined as abnormal.[33] Therefore, RSI may be considered a practical tool in the approach of patients with suspected LPR.[34]

Patients were stratified as having normal (≤13) or pathological (>13) RSI.

Statistical analysis

Continuous variables were reported as mean with standard deviation and categorical variables as the number of subjects and percentage values. The logistic Mixed-effect Regression Models (MRMs) were performed to assay the DED effect on the RSI. Moreover, an exploratory interaction analysis was used to test whether the DED's impact on the RSI was different according to age and gender.

The logistic and linear regression models were performed (logistic and linear family functions were used for continuous and count outcomes, respectively). Moreover, an interaction analysis was performed to test the intergroup impact of LPR on DED using the MRMs. Finally, an intragroup analysis was performed using the MRMs to assay the RSI effect on outcomes in the groups. The odd ratios and rate ratios associated with clinical outcomes were calculated with their 95% confidence interval for each factor from the MRMs. The Likelihood Ratio test was used as a test of statistical significance. The possible variability among clinical centers was considered adding the center variable as a random effect in all MRMs. Due to the exploratory nature of this study, adjustment for multiple testing was not performed. With a p-value less than 0.05, differences were selected as significant, and data were acquired and analyzed in R v4.0.3 software environment.[35]

Results

The two groups were well matched concerning age and sex ($p = .89$). Considering the RSI results as the primary variable in all patients, 80 (32.6%) patients had pathological (>13) RSI. In particular, RSI was positive in 68 (44.7%) patients with DED and 12 (12.9%) NEG subjects.

Association between the clinical conditions and the RSI

Table 1 reports the distribution of RSI results in the two groups. Pathological RSI was more frequent in DED (85%) than in NEG subjects (15%). The univariate analysis showed a significant association between pathological RSI and DED (OR = 8; 95% C.I. 3.84: 18.09; $p < .0001$).

As concerns the exploratory interaction analysis, age and gender did not affect RSI results (p-value for the interaction terms: 0.5022 and 0.9131, respectively; data not showed).

Table 1. Contingency tables and analysis output of the association between clinical conditions and RSI (N = 245). Characteristic: variable taken into account; OR (95% CI): Odd Ratio coefficient with 95% confidence interval.

	Descriptive statistics		Univariate analysis	
Characteristic	Normal RSI (≤13; n = 165)	Pathological RSI (>13; n = 80)	OR (95%CI)	p-value
Subjects				**<0.0001**
Comparison Group	81 (49.09%)	12 (15%)	1	
DED Patients	84 (50.91%)	68 (85%)	8 (3.84: 18.09)	

The RSI effects on ocular outcomes

Descriptive statistics of the RSI effect on the ophthalmological parameters in all patients are reported in Table 2. Patients with pathological RSI score had higher SANDE (Frequency and Severity) and OSDI values than patients with normal RSI score (63.07 *versus* 40.60, 59.44 *versus* 40.65, and 48.33 *versus* 29.12, respectively). In addition, the multivariate analysis showed that patients with pathological RSI had higher odds of having more impaired SANDE Frequency (OR = 13), SANDE Severity (OR = 10.55), and OSDI (OR = 9.44) scores than patients with normal RSI (p-values: 0.02, 0.01, and <0.001, respectively).

The RSI effect on ophthalmological outcomes *in* NEG subjects

Table 3 reports the effect of RSI in NEG subjects. Non-dry eye group subjects with pathological RSI had higher SANDE (Frequency and Severity), OSDI, and Schirmer scores than NEG subjects with normal RSI. The univariate analysis showed that NEG subjects with pathological RSI had a higher probability of having more impaired SANDE Frequency (OR = 16.36), SANDE Severity (OR = 14.51), OSDI (OR = 12.54), and Schirmer (7.22) scores than NEG subjects with normal RSI (p-values: 0.02, 0.03, <0.001, and 0.01, respectively).

Table 2. Descriptive statistics and multivariate analysis in all patients. Outcome = outcome taken into account; Descriptive statistics are reported as mean with standard deviation. Estimate (95%CI) = regression coefficient with 95% Confidence Interval (marked with *) and odd ratios, estimated using logistic (marked with ◊) were reported; p-value = the Likelihood Ratio p-value. In bold, the p-values below 0.05.

Outcome	*Normal* RSI (≤13; n = 165)	*Pathological* RSI (>13; n = 80)	Estimate (95%CI)		p-value
SANDE Frequency	40.6 (34.47)	63.07 (28.51)	13 (3.54: 22.45)	*	**0.02**
SANDE Severity	40.65 (33.71)	59.44 (29.09)	10.55 (2.6: 18.5)	*	**0.01**
OSDI	29.12 (24.48)	48.33 (24.09)	9.44 (4.36: 14.52)	*	**<0.001**
Schirmer	9.89 (7.31)	13.09 (10.25)	2.93 (−0.44: 6.3)	*	0.08
BUT	7.1 (4.9)	5.08 (3.98)	−0.03 (−1.09: 1.04)	*	0.96
Oxford-RE	0.66[1]	1.3 (1.17)	1.24 (0.87: 1.78)	◊	0.22
Oxford-LE	0.71 (1.11)	1.25 (1.15)	1.25 (0.87: 1.79)	◊	0.23

Table 3. The RSI descriptive statistics and the MRM output of outcomes in Comparison Group patients. Descriptive statistics are reported as mean with standard deviation. Estimate (95%CI) = regression coefficient with 95% Confidence Interval (marked with *) and odd ratios, estimated using logistic (marked with ◊) regression, were reported; p-value: Likelihood Ratio p-value for the interaction terms. In bold, the p-values below 0.05.

	Comparison Group subjects				
	Descriptive statistics		*Univariate analysis*		
Outcome	*Normal* RSI (≤13; n = 81)	*Pathological* RSI (>13; n = 12)	Estimate (95%CI)		p-value
SANDE Frequency	13.83 (15.77)	31.4[22]	16.36 (2.68: 30.04)	*	**0.02**
SANDE Severity	21.38 (23.42)	41.66 (32.24)	14.51 (0.82: 28.2)	*	**0.03**
OSDI	10.68 (7.79)	23.63 (26.09)	12.54 (5.43: 19.66)	*	**<0.001**
Schirmer	15.38 (4.33)	22.6 (7.83)	7.22 (1.62: 12.81)	*	**0.01**
BUT	10.86 (3.17)	10.5 (4.07)	0.98 (−1.53: 3.49)	*	0.5069
Oxford_RE	0.12 (0.33)	0.2 (0.45)	1.73 (0.2: 15.2)	◊	0.6434
Oxford_LE	0.16 (0.37)	0.2 (0.45)	1.38 (0.16: 12)	◊	0.7774

The RSI effect on ophthalmological outcomes in DED patients

Table 4 reports the effect of RSI in DED patients. DED patients with pathological RSI had higher OSDI scores than DED patients with normal RSI. The univariate analysis showed that DED patients with pathological RSI had a higher probability of having more impaired OSDI (OR = 8.75; p = .01) scores than DED patients with normal RSI.

Discussion

The present study showed that laryngopharyngeal reflux was commonly associated with DED, as about 45% of DED patients had suspected LPR. This outcome should be contextualized with a recent study reporting that up to 30% of the general population had LPR.[36] Even if LPR diagnosis is still problematic and challenging,[37] the RSI questionnaire is commonly considered a reliable tool for screening LPR in clinical practice.[38]

There is convincing evidence that LPR plays a role in airway inflammation involving some organs, such as the larynx, pharynx, paranasal sinus, and middle ear.[10,11,17,18,39] This concept paved the way to investigate a possible LPR impact also on the eye. In this regard, the presence of pepsin has been documented in tears.[18,19] Also, LPR is common in patients with ocular surface disease, mainly concerning DED.[20] Consistently, dry eye symptoms and pepsin in tears have been documented in LPR patients.[21] Therefore, these findings support the possible pathogenic association between DED and LPR.

Pepsin is a serine-protease able to unselectively cut portions of different proteins to promote their physiological digestion. However, outside the stomach, pepsin interferes with several molecular partners involved in the ocular surface's homeostasis, arousing mucosal damage. Consistently, the pepsin proteolytic activity promotes an inflammatory reaction, as elegantly documented.[21]

On the other hand, pepsin is active in an acidic milieu (usually between 1.8 and 4.4), as it occurs in the stomach. The ocular surface's physiologic pH does not arrive at values able to activate pepsin, but inflammatory events could drop pH to activating levels, as reported.[21] Moreover, it has been reported that pepsin can be endocytosed and consequently activated in the lysozymes at the larynx point.[40] The pathogenic mechanisms through which the ocular surface damage occurs could be translated by the evidence documented in other organs, including the lung and larynx.[41,42] In particular, pepsin causes a direct erosion of the mucosa that elicits hyperemia and irritative symptoms. Also, an *in vitro* study showed that the exposure of hypopharyngeal cells to pepsin in a nonacidic environment induced the expression of several pro-inflammatory cytokines and receptors (CCL20, CCL26, IL8, IL1F10, IL1A, IL5, BCL6, CCR6, and CXCL14), involved in reflux-dependent esophagitis.[43] This study prospected that nonacidic pepsin reflux, during maximal antiacid suppression, could still contribute to epithelial inflammation.[43] Therefore, it has been hypothesized that pepsin may promote pro-inflammatory cytokines in the ocular surface.[21] Another pathogenic mechanism includes the pepsin effect on mucus, as pepsin is a mucolytic agent and modulates the mucin gene in the digestive tract.[44,45] As a result, pepsin could affect the ocular mucus layer, impairing the tear film stability and protective defenses. These events lead to mucosal damage and inflammatory phenomena.

Notably, a recent experience demonstrated that a combined treatment, such as eye drops and tablets containing magnesium alginate, significantly improved symptoms and ophthalmological parameters in patients with DED due to LPR.[46] Thanks to its molecular egg-box structure, topical magnesium alginate can scavenger substances, including pepsin, inhibiting its proteolytic activity.[47] Alginate, orally-administered, is a fruitful medication in GERD management as it precipitates as a gel after exposure to the gastric acid, thus forming a raft that represents a barrier to the reflux of the gastric content into the oesophagus.[48] Based on this background, the current study aimed at investigating the prevalence of LPR and the possible clinical impact of LPR in DED patients. For this purpose, a multicenter study included eight ophthalmological clinics highly specialized in ocular surface diseases.

The primary outcome of this study showed that LPR commonly affects DED patients, as about 45% had suspected LPR. This high prevalence was significantly higher in comparison with about 13% in the comparison group. This result had a meaningful clinical relevance as DED patients had an eight times greater risk of presenting pathological RSI than NEG subjects. It means that nearly half of patients with DED are likely (OR = 8) to have laryngopharyngeal reflux. Moreover, LPR had a relevant impact on worsening ocular parameters in both DED and NEG subjects, mainly concerning OSDI and SANDE scores. It suggests that refluxate impairs the ocular surface. This finding was consistent with the previous studies that documented an aggressive role by refluxate in damaging ocular surface.[21] In particular, as DED is an inflammatory disease, LPR, inducing inflammation on the ocular surface, could be envisaged as a pathogenic factor. Consistently, DED patients with suspected LPR presented a more severe symptom perception than non-DED patients.

It also has to be noted that patients with normal RSI showed lower Schirmer's score, such as worse tear volume, than subjects with pathological RSI, including the overall population, DED group, and NEG group. This phenomenon could depend on hyperreactivity eliciting changes in tear production, but mechanistic studies should define this finding.

Table 4. The RSI descriptive statistics and the MRM output of outcomes in DED patients. Descriptive statistics are reported as mean with standard deviation. Estimate (95%CI) = regression coefficient with 95% Confidence Interval (marked with *) and odd ratios, estimated using logistic (marked with ◊) regression, were reported; *p*-value: Likelihood Ratio *p*-value for the interaction terms. In bold, the *p*-values below 0.05.

	DED patients			
	Descriptive statistics		*Univariate analysis*	
Outcome	*Normal* RSI (≤13; n = 84)	*Pathological* RSI (>13; n = 68)	Estimate (95%CI)	p-value
SANDE Frequency	60.46 (30.97)	66.31 (27.24)	9.72 (−1.97: 21.42) *	0.15
SANDE Severity	59.22 (31.71)	62.68 (27.53)	6.65 (−3.42: 16.73) *	0.33
OSDI	46.9 (21.78)	52.69 (21.08)	8.75 (1.9: 15.6) *	**0.01**
Schirmer	6.92 (6.9)	10.44 (9.35)	0.47 (−3.62: 4.57) *	0.77
BUT	4.19 (3.13)	4.29 (3.33)	0.21 (−0.94: 1.37) *	0.73
Oxford_RE	1.16 (1.14)	1.39 (1.17)	1.22 (0.85: 1.75) ◊	0.26
Oxford_LE	1.21 (1.3)	1.34 (1.15)	1.21 (0.83: 1.75) ◊	0.32

The current study had some limitations, including the retrospective design and the lack of a documented LPR diagnosis. However, RSI is an excellent tool to suspect LPR.[49] Moreover, the comparison group included patients with ocular disorders, so they cannot be considered ideal controls, such as healthy subjects. However, the present non-dry eye group included patients with refractive problems, age- and sex-matched, and recruited in everyday practice; thus, the comparison could be legitimate. It has to be highlighted that there was a prevalence of females, it can attribute to a confounding effect, namely dry eye disease is more likely to affect the female sex. In addition, fluorescein BUT was used instead of non-invasive procedures as it is routinely employed in the clinical practice of the participant centers.

Further studies with rigorous methodology will be welcome to identify the exact nature of the association between DED and LPR, as suggested by these results. In addition, investigating biomarkers on DED patients' ocular surface with and without LPR could also help understand the mechanistic phenomenon involved in that unexpected association.

In conclusion, the current study showed that LPR was more common in DED patients than in other patients seen in an ophthalmological clinic (45% versus 13%, i.e., OR = 8). Furthermore, laryngopharyngeal reflux is associated with the worst symptom perception in DED and patients with an ocular problem. Therefore, LPR appears as a condition often associated with DED and a potential risk factor for increasing disease burden. However, whether LPR is directly a causative agent of DED and LPR management improves DED conditions remains to be clarified in further prospective studies.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The study had no funding.

ORCID

G. Ciprandi http://orcid.org/0000-0001-7016-8421

References

1. Clayton JA. Dry eye. New England J Med. 2018;378:2212–23. doi:10.1056/NEJMra1407936.
2. Wolffsohn JS, Arita R, Chalmers R, Djalilian A, Dogru M, Dumbleton K, Gupta PK, Karpecki P, Lazreg S, Pult H, et al. TFOS DEWS II diagnostic methodology report. Ocul Surf. 2017;15:539–74.
3. Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo C-K, Liu Z, Nelson JD, Nichols JJ, Tsubota K, et al. TFOS DEWS II definition and classification report. Ocul Surf. 2017;15:276–83. doi:10.1016/j.jtos.2017.05.008.
4. Rosenfield M. Computer vision syndrome: a review of ocular causes and potential treatments. Ophthalmic Physiol Opt. 2011;31:502–15. doi:10.1111/j.1475-1313.2011.00834.x.
5. Choi JH, Li Y, Kim SH, Jin R, Kim YH, Choi W, You IC, Yoon KC. The influences of smartphone use on the status of the tear film and ocular surface. PlosOne. 2018;13:e0206541. doi:10.1371/journal.pone.0206541.
6. Messmer EM. The pathophysiology, diagnosis, and treatment of dry eye disease. Dtsch Arztebl Int. 2015;112:71–82.
7. Marshall LL, Roach JM. Treatment of dry eye disease. Consult Pharm. 2016;31:96–106. doi:10.4140/TCP.n.2016.96.
8. Gomes JAP, Azar DT, Baudouin C, Efron N, Hirayama M, Horwath-Winter J, Kim T, Mehta JS, Messmer EM, Pepose JS, et al. TFOS DEWS II iatrogenic report. Ocul Surf. 2017;15(3):511–38.
9. Mittal R, Vaezi MF. Esophageal motility disorders and gastroesophageal reflux disease. N Engl J Med. 2020;383(20):1961–197. doi:10.1056/NEJMra2000328.
10. Salihefendic N, Zidzic M, Cabric E. Laryngopharyngeal reflux disease – LPRD. Med Arch. 2017;71:215–18. doi:10.5455/medarh.2017.71.215-218.
11. Capagnolo AM, Priston J, Heidrichthoen R, Medeiros T, Assuncao RA. Laryngopharyngeal reflux: diagnosis, treatment, and latest research. Int Arch Otorhinolaryngol. 2014;18:184–91.
12. Koufman JA. Laryngopharyngeal reflux: position statement of the committee on speech, voice and swallowing disorders of the American Academy of Otolaryngology-Head and Neck Surgery. Otolaryngol Head Neck Surg. 2002;217:32–35. doi:10.1067/mhn.2002.125760.
13. Francis DO, Rymer JA, Slaughter JC, Choksi Y, Jiramongkolchai P, Ogbeide E, Tran C, Goutte M, Garrett CG, Hagaman D, et al. High economic burden of caring for patients with suspected extraesophageal reflux. Am J Gastroenterol. 2013;108(6):905–11. doi:10.1038/ajg.2013.69.
14. Bulmer DM, Ali MS, Brownlee IA, Dettmar PW, Pearson JP. Laryngeal mucosa: its susceptibility to damage by acid and pepsin. Laryngoscope. 2010;120(4):777–82. doi:10.1002/lary.20665.
15. Adhami T, Goldblum JR, Richter JE, Vaezi MF. Role of gastric and duodenal ingredients in laryngeal tissue injury: an experimental study in dogs. Am J Gastroenterol. 2004;99:2098–106. doi:10.1111/j.1572-0241.2004.40170.x.
16. Johnston N, Wells CW, Samuels TL, Blumin JH. Pepsin in non-acid refluxate can damage hypopharyngeal epithelial cells. Ann Otol Rhinol Laryngol. 2009;118:677–85. doi:10.1177/000348940911800913.
17. Gelardi M, Ciprandi G. Focus on gastroesophageal reflux (GER) and laryngopharyngeal reflux (LPR): new pragmatic insights in clinical practice. J Biol Regul Homeost Agents. 2018;32:41–47.
18. Magliulo G, Plateroti R, Plateroti AM. Gastroesophageal reflux disease and the presence of pepsin in the tears. Med Hypotheses. 2013;80(2):129–30. doi:10.1016/j.mehy.2012.11.008.
19. Iannella G, Di Nardo G, Plateroti R, Rossi P, Plateroti AM, Mariani P, Magliulo G. Investigation of pepsin in tears of children with laryngopharyngeal reflux disease. Int J Pediatr Otorhinolaryngol. 2015;79(12):2312–15. doi:10.1016/j.ijporl.2015.10.034.
20. Mazzacane D, Damiani V, Silvestri M, Ciprandi G, Marino P. Eye reflux: an ocular extraesophageal manifestation of gastric reflux. Int J Ophthalmol. 2018;11:1503–07.
21. Plateroti R, Sacchetti M, Magliulo G, Plateroti AM, Pace A, Moramarco A, Lambiase A, Bruscolini A. Evidence of pepsin-related ocular surface damage and dry eye (PROD syndrome) in patients with laryngopharyngeal reflux. Life. 2020;10:202. doi:10.3390/life10090202.
22. Schaumberg DA, Gulati A, Mathers WD, Clinch T, Lemp MA, Nelson JD, Foulks GN, Dana R. Development and validation of a short global dry eye symptom index. Ocul Surf. 2007;5:50–57. doi:10.1016/S1542-0124(12)70053-8.
23. Walt JG, Rowe MM, Stern KL. Evaluating the functional impact of dry eye: the ocular surface disease index. Drug Int J. 1997;31:1436.
24. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the ocular surface disease index. Arch Ophthalmol. 2000;118(5):615–21. doi:10.1001/archopht.118.5.615.
25. Pakdel F, Gohari MR, Jazayeri AS, Amani A, Pirmarzdashti N, Aghaee H. Validation of farsi translation of the ocular surface disease index. J Ophthalmic Vis Res. 2017;12(3):301–04. doi:10.4103/jovr.jovr_92_16.
26. Versura P, Frigato M, Bernabini B, Mulè R, Malavolta N, Campos EC. Ocular surface analysis in patients affected with rheumatic diseases. Reumatismo. 2004;56:262–71.

27. Miller KL, Walt JG, Mink DR, Satram-Hoang S, Wilson SE, Perry HD, Asbell PA, Pflugfelder SC. Minimally clinically important difference for the ocular surface disease index. Arch Ophthalmol. 2010;128:94–101. doi:10.1001/archophthalmol.2009.356.
28. O'Brien PD, Collum LM. Dry eye: diagnosis and current treatment strategies. Curr Allergy Asthma Rep. 2004;4(4):314–19. doi:10.1007/s11882-004-0077-2.
29. Mengher LS, Bron AJ, Tonge SR, Gilbert DJ. A non-invasive instrument for clinical assessment of the pre-corneal tear film stability. Curr Eye Res. 1985;4:1–7. doi:10.3109/02713688508999960.
30. Stevens S. Schirmer's test. Comm Eye Health. 2011;24:45.
31. Bron AJ, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. Cornea. 2003;22:640–50. doi:10.1097/00003226-200310000-00008.
32. Chun YS, Park IK. Reliability of 4 clinical grading systems for corneal staining. Am J Ophthalmol. 2014;157:1097–102. doi:10.1016/j.ajo.2014.02.012.
33. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). J Voice. 2002;16(2):274–77. doi:10.1016/S0892-1997(02)00097-8.
34. Campagnolo AM, Priston J, Thoen RH, Medeiros T, Assunção AR. Laryngopharyngeal reflux: diagnosis, treatment, and latest research. Int Arch Otorhinolaryngol. 2014;18:184–91.
35. R Core Team. R: a language and environment for statistical computing. Vienna (Austria): R Foundation for Statistical Computing; 2021. [accessed 2021 May 30]. https://www.R-project.org/ .
36. Reiter R, Heyduck A, Seufferlein T, Hoffmann T, Pickhard A. Laryngopharyngeal reflux. Laryngorhinootologie. 2018;97(4):238–45. doi:10.1055/s-0044-100794.
37. Runggaldier D, Hente J, Brockmann-Bauser M, Runggaldier D, Hente J, Brockmann-Bauser M, Pohl D, Bohlender JE. Current possibilities and challenges in the diagnosis of laryngopharyngeal-reflux]. HNO; 2021. (in press).
38. Silva ÁS, Duprat AC, Machado SR, Melo DN, Nascimento Ribeiro DK. Evaluation of the reflux symptom index and the endolaryngeal findings scale after treatment in individuals with laryngopharyngeal reflux. Int Arch Otorhinolaryngol. 2021;25(1):e115–e122. doi:10.1055/s-0040-1702967.
39. Ciprandi G, Gelardi M. Gastric reflux: comparison between the gastroenterologist and the otorhinolaryngologist's approach. Pragmatic conclusive remarks. J Biol Regul Homeost Agents. 2018;32:33–38.
40. Johnston N, Dettmar PW, Bishwokarma B, Lively MO, Koufman JA. Activity/stability of human pepsin: implications for reflux attributed laryngeal disease. Laryngoscope. 2007;117:1036–39. doi:10.1097/MLG.0b013e31804154c3.
41. Kim Y, Lee Y, Cho YJ, Yoon HI, Lee JH, Lee CT, Park JS. Association between pepsin in bronchoalveolar lavage fluid and prognosis of chronic fibrosing interstitial lung disease. Tohoku J Exp Med. 2018;246:147–53. doi:10.1620/tjem.246.147.
42. Wang L, Tan JJ, Wu T, Zhang R, Wu JN, Zeng -F-F, Liu Y-L, Han X-Y, Li Y-F, Li X-P. Association between laryngeal pepsin levels and the presence of vocal fold polyps. Otolaryngol Head Neck Surg. 2017;156:144–51. doi:10.1177/0194599816676471.
43. Samuels TL, Johnston N. Pepsin as a causal agent of inflammation during nonacidic reflux. Otolaryngol Head Neck Surg. 2009;141:559–63. doi:10.1016/j.otohns.2009.08.022.
44. Allen A, Pearson JP, Blackburn A, Coan RM, Hutton DA, Mall AS. Pepsins and the mucus barrier in peptic ulcer disease. Scand J Gastroenterol. 1988;23:50–57. doi:10.3109/00365528809099130.
45. Samuels TL, Handler E, Syring ML, Pajewski NM, Blumin JH, Kerschner JE, Johnston N. Mucin gene expression in human laryngeal epithelia: effect of laryngopharyngeal reflux. Ann Otol Rhinol Laryngol. 2008;117:688–95. doi:10.1177/000348940811700911.
46. Balestrazzi A, Passali GC, Passali D, Damiani V, Ciprandi G, Balestrazzi E. A new therapeutic approach for the Dry Eye Syndrome in patients with laryngopharyngeal reflux: first data. Acta Biomed. 2020;91:36–42.
47. Wan LQ, Jiang J, Arnold DE, Guo XE, Lu HH, Mow VC. Calcium concentration effects on the mechanical and biochemical properties of chondrocyte-alginate constructs. Cell Mol Bioeng. 2008;1:93–102. doi:10.1007/s12195-008-0014-x.
48. Davies I, Burman-Roy S, Murphy MS, Guideline Development Group. Gastroesophageal reflux disease in children: NICE guidance. BMJ. 2015;350:g7703. doi:10.1136/bmj.g7703.
49. Nacci A, Bastiani L, Barillari MR, Lechien JR, Martinelli M, de Bortoli N, Berrettini S, Assessment FB. Diagnostic accuracy evaluation of the reflux symptom index (RSI) scale: psychometric properties using optimal scaling techniques. Ann Otol Rhinol Laryngol. 2020;129(10):1020–29. doi:10.1177/0003489420930034.