

The relationship between clinical signs and dry eye symptoms

H Pult^{1,2}, C Purslow² and PJ Murphy²

Abstract

Purpose To evaluate (i) the relationship between traditional and new clinical tests (lid-wiper epitheliopathy (LWE), lid-parallel conjunctival folds (LIPCOF)) and dry eye symptoms in non-contact lens wearers, and (ii) that a combination of these tests can improve predictive ability for the development of dry eye symptoms.

Methods Tear meniscus height (TMH), non-invasive break-up time (NIBUT), ocular hyperaemia, LIPCOF, phenol red thread test (PRTT), corneal and conjunctival staining, and LWE grades were observed in a cohort of 47 healthy, non-lens wearers (male = 17, female = 30, median age = 35 years, range = 19–70). Symptoms were assessed using the Ocular Surface Disease Index (OSDI).

Results LWE was significantly correlated to both temporal and nasal LIPCOF ($0.537 < r < 0.607$, $P < 0.05$). LIPCOF and LWE were significantly correlated to NIBUT and PRTT ($r > -0.248$, $P < 0.001$). Significant correlations were found between NIBUT and TMH ($r = 0.461$, $P = 0.001$) and PRTT ($r = 0.640$, $P < 0.001$). OSDI scores were significantly correlated to NIBUT, TMH, PRTT, LIPCOF, and LWE ($r > |0.31|$; $P < 0.05$). Significant discriminators of OSDI +/– were NIBUT (area under the receiver operative characteristic curve (AUC) = 0.895), TMH (0.715), PRTT (0.781), LIPCOF (temporal/nasal/Sum 0.748/0.828/0.816), and LWE (0.749). Best predictive ability was achieved by combining NIBUT with nasal LIPCOF (AUC = 0.944).

Conclusions The individual tests NIBUT, TMH, PRTT, LIPCOF, and LWE were significantly, but moderately, related to OSDI scores. The strongest relationship appeared by combining NIBUT with nasal LIPCOF.

Eye (2011) 25, 502–510; doi:10.1038/eye.2010.228; published online 21 January 2011

Keywords: lid-parallel conjunctival folds; LIPCOF; lid-wiper epitheliopathy; dry eye; NIBUT

Introduction

Many patients suffer from ocular-related symptoms, such as stinging, burning, itching, light sensitivity, and blurry vision,^{1–5} which limit the quality of life, as well as occupational productivity.^{6,7} Correlations between these symptoms and individual clinical dry eye tests, like meibomian gland assessment, tear meniscus height (TMH) measurement, tear break-up time, phenol red thread test, Schirmer test, ocular staining, and ocular hyperaemia, are frequently poor.^{8–11}

A combination of tests might improve analysis of dry eye,^{9,12–14} but there is no agreement on which combination provides the best results.^{11,12} New clinical tests, such as lid-wiper epitheliopathy (LWE)¹⁵ and lid-parallel conjunctival folds (LIPCOF),^{13,16–19} show promising predictive ability for dry eye. Combining the clinical grading of temporal and nasal LIPCOF to produce a new score (named LIPCOF Sum) has shown useful predictive ability for dry eye symptoms in experienced soft contact lens wearers,¹⁹ as well as in naive contact lens wearers.¹³ The benefit of this test combination in examining a healthy non-contact lens wearing population is unknown.

LWE is a clinically observable alteration in the epithelium of the lid wiper, which is that portion of the marginal conjunctival epithelium of the upper eyelid that wipes the ocular surface during blinking. In patients with dry eye, the tear film is thought to be insufficient to separate the ocular surface and lid wiper.¹⁵ Because of this deficiency, the lid wiper is subjected to trauma during blinking, as a result of the continual rubbing of the narrow surface area of lid wiper tissue against the corneal surface.^{15,18–20}

LIPCOF are sub-clinical folds in the temporal and nasal lower quadrants of the bulbar conjunctiva, parallel to the lower lid margin, easily observable by slit-lamp biomicroscope

¹Optometry and Vision Research, Weinheim, Germany

²School of Optometry and Vision Sciences, Contact Lens and Anterior Eye Research (CLAER) Unit, Cardiff University, Wales, UK

Correspondence: H Pult, Optometry and Vision Research, Steingasse 15, Weinheim 69469, Germany
 Tel: +49 (0) 174 902 5090;
 Fax: +49 (0) 620 187 3657.
 E-mail: ovr@heiko-pult.de

Received: 13 August 2010
 Accepted in revised form: 2 December 2010
 Published online: 21 January 2011

(Figure 1).^{13,16–19} Bulbar conjunctival folds were first described by Hughes *et al*²¹ and named conjunctivochalasis and they have been reported in severe dry eye patients.^{22–36} LIPCOF might represent the first mild stages of conjunctivochalasis and thus share the same aetiology. Several causes of bulbar conjunctival folds are hypothesised: conjunctival ‘looseness’ as a result of inflammatory processes,^{23,27,36} a decrease of elastic fibres,^{27,36} aging,^{25,27} or lymphatic dilation by mechanical forces between the lower lid and conjunctiva that gradually interferes with lymphatic flow.³¹ Increased friction in blinking might follow from insufficient mucins, or an altered composition of the resident mucins at the ocular surface.^{17–19}

Whilst LWE has been reported to be predictive of dry eye symptoms in non-lens wearers and contact-lens wearers,¹⁵ it is not known how LIPCOF relates to symptoms in healthy non-contact lens wearers. An appraisal of these signs may form an important part of any assessment amongst the general population. This study aimed to (i) analyse the relationships between the results of clinical tests and ocular signs, as well as symptoms, and (ii) evaluate the usefulness of such clinical tests in detecting the early stages of dry eye in healthy non-contact lens wearers.

Materials and methods

Forty-seven healthy, non-lens wearers (male = 17, female = 30, median age_{all} = 35 years, range_{all} = 19–70 (median age_{male} = 34.6 years, median age_{female} = 36.3)) who had never worn contact lenses previously were selected from volunteers attending the optometry practice of Horst Riede GmbH, Weinheim, Germany for a routine eye exam. The tear film characteristics and ocular

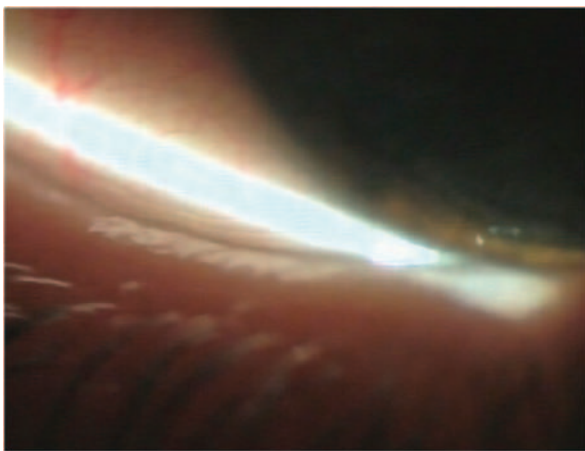


Figure 1 Two parallel conjunctival folds at the temporal quadrant of the eye (LIPCOF grade 2).

surface of the eyes were evaluated during a single clinical session and subjects asked to complete the Ocular Surface Disease Index (OSDI) questionnaire. Symptoms were masked for the observer, as well as the result of slit-lamp microscope evaluation for the subjects. All measures were conducted on the right eye only.

Inclusion and exclusion criteria

Subjects were excluded if they had Sjögren’s syndrome, rheumatoid arthritis, diabetes, recent ocular infections, hay fever, any history of ocular surgery, use of any medication or eye drops known to affect the ocular surface, worn contact lenses or had contact lens experiences, or were pregnant. All procedures were conducted in accordance with the Declaration of Helsinki (1983), and approval for the study was given by the Cardiff School of Optometry and Vision Sciences Ethics Committee. All subjects gave written informed consent before participating in the study.

Techniques

Tear meniscus height

TMH was measured by a slit-lamp microscope (with a graticule in 0.05 mm units) at the centre of the lower lid margin. The slit was positioned horizontal to the lower lid with indirect illumination, to exclude invasive triggers like glaring or heating. Three consecutive readings were evaluated and the median noted.

Non-invasive break-up time (NIBUT)

NIBUT was determined non-invasively using a TearScope Plus (Keeler Ltd., Windsor, UK) with a fine grid insert.³⁷ NIBUT was the time measured, in seconds, between the full opening of the eyelids after a complete blink and the first break in the tear film (using the included stop-watch of the TearScope Plus). Three consecutive readings were evaluated and the median noted.

Ocular hyperaemia

Limbal and bulbar hyperaemia of the horizontal segment of the ocular surface was evaluated by slit-lamp microscope using 12 × magnification and classified using the CCLRU grading scale (University of New South Wales, Sydney, Australia),^{38–40} interpolated in 0.1 increments.

Lid-parallel conjunctival folds

LIPCOF was evaluated in the area perpendicular to the temporal and nasal limbus on the bulbar conjunctiva above the lower lid (temporal and nasal LIPCOF,

respectively) with a slit-lamp microscope using 18–24 × magnification as necessary,^{13,17–19} and classified using the optimised grading scale (Table 1).^{13,17–19} A further combined LIPCOF score (LIPCOF Sum) was calculated by adding together the nasal LIPCOF grade and temporal LIPCOF grade.¹⁹ Care was taken to differentiate between parallel, permanent conjunctival folds (LIPCOF) and disrupted micro-folds.^{13,17–19,41–45}

Phenol red thread test (PRTT)

Subjects were asked to keep their eyes open (blinking gently, if necessary) for 15 s while a phenol red-impregnated cotton thread (Zone-Quick; Menicon Co. Ltd., Nagoya, Japan) was placed in the lower conjunctival sac. This test is based on the Hamano cotton thread test measuring tear volume in the lower meniscus sac.⁴⁶ Since the PRTT can effectively differentiate between aqueous deficient and non-aqueous deficient dry eye⁴⁷ it was used in this study as a surrogate of the Schirmer test I, being less invasive.

Corneal and conjunctival staining

Conjunctival and corneal staining were assessed by applying 1% lissamine green and 2% fluorescein, and classified into four grades, interpolated in 0.1 increments (CCLRU grading scale).^{38–40} The fluorescein grading scale was used for both measures in the absence of a published recommendation for lissamine green staining.

Lid-wiper epitheliopathy (LWE)

LWE was made visible using a combination of instilled 1% lissamine green and 2% fluorescein, and evaluated for the upper lid. A second instillation of both dyes was carried out after 5 min.⁴⁸ LWE was observed using a slit-lamp microscope with 18 × magnification, classified according to Korb *et al.*^{15,20} Care was taken to differentiate between the fluorescein and lissamine staining associated with Marx’s line and that from staining of the lid wiper.^{15,20}

Ocular Surface Disease Index

Each subject’s symptoms were evaluated after objective observation by a validated German translation of the

Table 1 Optimised grading scale of LIPCOF^{13,18,19}

	LIPCOF grade
No conjunctival folds	0
One permanent and clear parallel fold	1
Two permanent and clear parallel folds, (normally <0.2 mm)	2
More than two permanent and clear parallel folds, (normally >0.2 mm)	3

Abbreviation: LIPCOF, lid-parallel conjunctival fold.

OSDI questionnaire.⁴⁹ Total OSDI scores were calculated as recommended by Schiffman *et al.*³

$$OSDI = \frac{\text{sum of scores} \times 25}{\text{number of questions answered}}$$

Statistical analyses

Data were examined for normality by Kolmogorov–Smirnov test and appropriate statistical tests used. Correlations between tear film tests were evaluated by Pearson correlation or Spearman rank, if variables were parametric or non-parametric, respectively; differences were evaluated using Mann–Whitney *U*-test. Best test combination was calculated by logistic regression analyses (forward: likelihood ratio (LR)). Discrimination and predictive ability of test/test combinations were analysed by receiver operative characteristic curve (ROC). The data were analysed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA) and BiAS 8.4.2 (Epsilon Verlag, Frankfurt, Germany).

Results

Significant correlations were observed between the clinical measures NIBUT, PRTT, LIPCOF, LWE, bulbar hyperaemia, and age ($-0.364 < r < 0.454$; $P < 0.034$; Table 2), but the effect of gender was not significant with any clinical measure (*U*-test, $P > 0.05$). Both temporal and nasal LIPCOF were significantly correlated to bulbar hyperaemia ($0.293 < r < 0.492$, $P < 0.023$), while only temporal LIPCOF was related to limbal hyperaemia ($r = 0.288$, $P = 0.025$). LWE was significantly correlated to both temporal and nasal LIPCOF ($0.537 < r < 0.607$, $P < 0.001$). NIBUT and PRTT were significantly negatively correlated to LIPCOF and LWE ($-0.479 < r < -0.248$, $P < 0.05$). Only NIBUT was significantly negatively correlated to bulbar hyperaemia (Pearson, $r = -0.492$, $P = 0.018$). NIBUT was significantly correlated to PRTT ($r = 0.640$, $P < 0.001$) and TMH (Spearman rank, $r = 0.461$, $P = 0.001$).

The tear film tests NIBUT, TMH, and PRTT, as well the ocular signs LIPCOF (temporal, nasal, Sum) and LWE, were significantly correlated to OSDI scores ($-0.591 < r < 0.586$; $P < 0.019$; Table 3, Figures 2 and 3).

Subjects were grouped by the OSDI score into 20 OSDI+ and 27 OSDI– by a cut-off value of 15 (ref. 3) and the ability of the tests to discriminate between OSDI+ (median OSDI score = 4.2) and OSDI– (median OSDI score 18.8) was evaluated by ROC. The tear film tests NIBUT, TMH, and PRTT were significant discriminators between groups, as well as the ocular signs LIPCOF (temporal, nasal, Sum) and LWE ($P < 0.01$; Tables 4 and 5). NIBUT was the best discriminator of the set of

Table 2 Correlations between tests of only the right eye, (r-value)

	Age	TMH	NIBUT	Temporal LIPCOF	Nasal LIPCOF	Bulbar hyperaemia	Limbal hyperaemia	PRTT	Corneal staining	Conjunctival staining	LWE
TMH	-0.145										
NIBUT	-0.364*	0.461*									
Temporal LIPCOF	0.284	0.046	-0.359*								
Nasal LIPCOF	0.454*	-0.149	-0.479*	0.592*							
Bulbar hyperaemia	0.360*	-0.004	-0.307*	0.492*	0.293						
Limbal hyperaemia	0.047	0.044	-0.101	0.288	0.028	0.673					
PRTT	-0.437*	0.375*	0.640*	-0.248	-0.402	-0.255	0.012				
Corneal staining	-0.188	-0.018	-0.043	0.002	0.063	-0.006	0.161	-0.075			
Conjunctival staining	-0.049	0.048	0.041	0.043	-0.163	-0.038	-0.108	0.110	-0.080		
LWE	0.340*	-0.146	-0.419*	0.537*	0.607*	0.275	-0.068	-0.390	0.058	0.163	

Abbreviations: LIPCOF, lid-parallel conjunctival fold; LWE, lid-wiper epitheliopathy; NIBUT, non-invasive break-up time; PRTT, phenol red thread test; TMH, tear meniscus height.

*Significant after Bonferroni adjustment.

Correlation coefficients in bold indicate significance levels were $0.001 < P > 0.042$.

Table 3 Correlations between tests and symptoms

	OSDI score	
	r	P
TMH	-0.450	0.001*
NIBUT	-0.591	<0.001*
Temporal LIPCOF	0.305	0.019
Nasal LIPCOF	0.586	<0.001*
LIPCOF Sum	0.427	0.001*
PRTT	-0.407	0.002*
Bulbar hyperaemia	0.229	0.061
Limbal hyperaemia	0.046	0.379
Corneal staining	0.012	0.469
Conjunctival staining	0.060	0.344
LWE	0.453	0.001*

Abbreviations: LIPCOF, lid-parallel conjunctival fold; LWE, lid-wiper epitheliopathy; NIBUT, non-invasive break-up time; PRTT, phenol red thread test; OSDI, Ocular Surface Disease Index; TMH, tear meniscus height.

*Significant after Bonferroni adjustment.

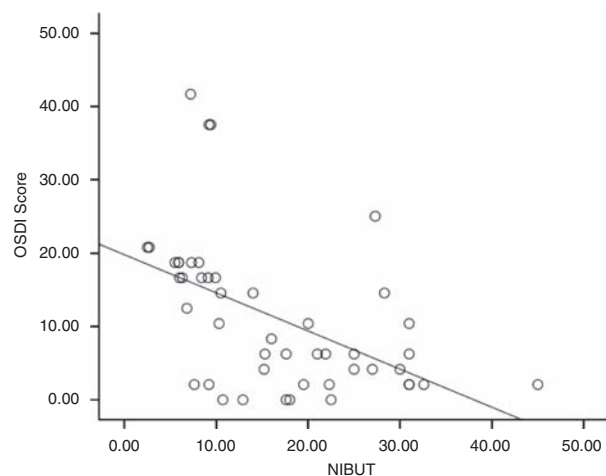


Figure 2 NIBUT was significantly correlated to OSDI scores.

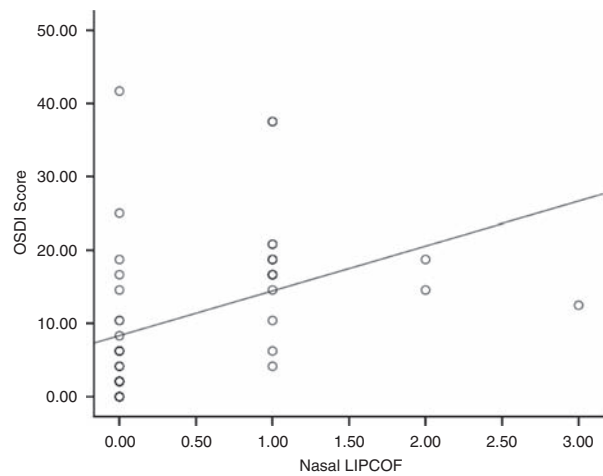


Figure 3 Nasal LIPCOF was significantly correlated to OSDI scores.

tear film tests with an area under the ROC (AUC) of 0.895 and nasal LIPCOF was the best discriminator of the ocular signs (AUC = 0.828). A combination of NIBUT and nasal LIPCOF resulted in an improved predictive ability (AUC = 0.94; Figure 4).

$$\text{OSDI} + / - = -0.227 \times \text{NIBUT} + 2.841 \\ \times \text{nasal LIPCOF} + 1.816$$

This test combination, here named Dry Eye Test Combination (DTC), was significantly correlated to OSDI scores (Pearson, $r = 0.558$, $P < 0.001$) (Figure 5). The power calculation of the completed study resulted in a power of > 0.92 .

Table 4 Area under the ROC (AUC), P-value (P), 95% confidence interval of AUC, threshold (TH), sensitivity, and specificity

	AUC	P	95% Confidence interval		TH	Sensitivity	Specificity
TMH	0.715	0.013	0.565	0.865	0.2 (ref. 66)	0.65	0.65
NIBUT	0.895	<0.001	0.791	1.000	10.0 (ref. 65)	0.80	0.93
Temporal LIPCOF	0.748	0.004	0.603	0.893	2 (ref. 19)	0.60	0.81
Nasal LIPCOF	0.828	<0.001	0.698	0.957	1 (ref. 19)	0.73	0.91
LIPCOF Sum	0.816	<0.001	0.687	0.945	2 (ref. 19)	0.70	0.81
Bulbar hyperaemia	0.664	0.057	0.501	0.827	2.35 ^a	—	—
Limbal hyperaemia	0.509	0.914	0.341	0.678	2.05 ^a	—	—
PRTT	0.781	0.001	0.642	0.919	10 (ref. 70)	0.25	0.93
Corneal staining	0.519	0.830	0.349	0.688	0.1 ^a	—	—
Conjunctival staining	0.506	0.949	0.337	0.674	1.0 ^a	—	—
LWE	0.749	0.004	0.597	0.901	1 (ref. 19)	0.48	0.96
Dry eye test combination	0.944	<0.001	0.865	1.024	-0.19 ^a	0.90	0.89

Abbreviations: LIPCOF, lid-parallel conjunctival fold; LWE, lid-wiper epitheliopathy; NIBUT, non-invasive break-up time; PRTT, phenol red thread test; TMH, tear meniscus height.

^aThresholds derived from this data set.

Table 5 Median scores, interquartiles of the significant discriminators of OSDI + / -

	Normal		Dry eye	
	Median	Interquartiles	Median	Interquartiles
TMH	0.20	0.20–0.30	0.18	0.10–0.20
NIBUT	21.00	15.30–30.00	7.70	5.93–9.78
PRTT	22.00	16.00–23.00	10.00	14.5–17.75
Temporal LIPCOF	1.00	0.00–1.00	2.00	1.0–2.0
Nasal LIPCOF	0.00	0.00–0.00	1.00	0.25–1.00
LIPCOF Sum	1.00	0.00–2.00	3.00	2.00–3.00
LWE	0.00	0.00–0.00	0.75	0.00–2.00

Abbreviation: LIPCOF, lid-parallel conjunctival fold; LWE, lid-wiper epitheliopathy; NIBUT, non-invasive break-up time; PRTT, phenol red thread test; OSDI, Ocular Surface Disease Index; TMH, tear meniscus height.

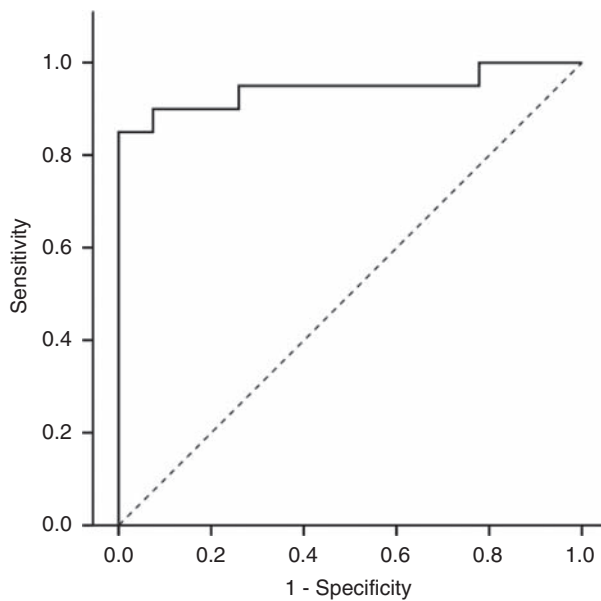


Figure 4 Discrimination of dry eye symptoms by a combination of NIBUT and nasal LIPCOF.

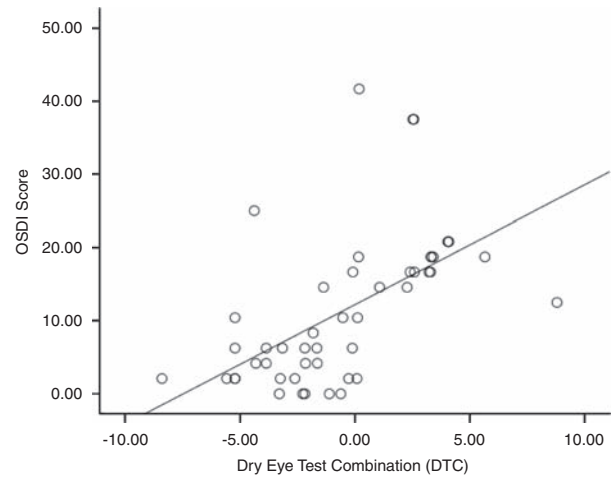


Figure 5 NIBUT combined with nasal LIPCOF was significantly correlated to OSDI scores.

Discussion

The subjects in this sample of a cohort of non-contact lens wearers presented with ocular signs within a relatively normal range (Table 6). The evaluated low LWE grades (77% ≤ 1) are comparable to values reported by Korb *et al*,¹⁵ where 82% of the subjects presented with LWE grade ≤ 1. The bulbar hyperaemia median score (CCLRU 2.3) and limbal hyperaemia median scores (CCLRU 2.0) were slightly higher than published norms, but within normal confidence limits.^{39,50} Median ocular staining of this cohort was at a normal level.^{38,51,52} For LIPCOF, this is the first time that median scores have been reported in non-contact lens wearers (1/0/1 (temporal/nasal/Sum)), which is less than that reported in experienced soft contact lens wearers (2/0/2).^{17,19} Interestingly, while the prevalence of dry eye is known to be increased in elderly women,^{53,54} no gender bias was found in the tests

Table 6 Median scores, interquartiles and range (min–max) of clinical tests

	Median	Inter-quartiles	Minimum	Maximum
TMH	0.20	0.15–0.30	0.05	0.40
NIBUT	15.20	8.10–25.00	2.50	45.00
PRTT	18.00	12.00–22.00	7.00	30.00
Temporal LIPCOF	1.00	0.00–2.00	0.00	3.00
Nasal LIPCOF	0.00	0.00–1.00	0.00	3.00
LIPCOF Sum	1.00	0.00–3.00	0.00	5.00
Bulbar hyperaemia	2.30	1.80–2.80	1.20	3.20
Limbal hyperaemia	2.00	1.80–2.80	1.00	3.60
Corneal staining	0.00	0.00–0.00	0.00	1.74
Conjunctival staining	0.00	0.00–0.00	0.00	3.00
LWE	0.00	0.00–0.50	0.00	3.00
OSDI score	8.33	2.08–16.67	0.00	41.67

Abbreviations: LIPCOF, lid-parallel conjunctival fold; LWE, lid-wiper epitheliopathy; NIBUT, non-invasive break-up time; PRTT, phenol red thread test; OSDI, Ocular Surface Disease Index; TMH, tear meniscus height.

in this study. This may be due to the mild nature of the dry eye symptoms reported by this subject cohort.

Both temporal and nasal LIPCOF were significantly correlated to LWE, as well as to ocular hyperaemia, whereas nasal LIPCOF was able to do so for bulbar hyperaemia only. In addition, LWE and LIPCOF were significantly correlated to tear film stability and tear volume. These findings reflect the hypothesised mechanical origin of LIPCOF and LWE.^{15,17–19} In LWE, squamous cells are visible at the lid wiper, which is in contact with the bulbar conjunctiva where the tear film is insufficient¹⁵ and/or reduced mucin quantity exists.^{17,18} Squamous epithelial cells are a feature of tissues that experience frequent rubbing,¹⁵ and their presence in the particular region of the lid wiper⁵⁵ infers that this area of the marginal conjunctiva is intimately and mechanically associated with the surfaces of the oculus bulbi.

Tear film volume is reported to be an important contributor to a stable tear film,^{47,56–59} and in this study the positive correlations observed between NIBUT and both TMH and PRTT strengthens this theory. Mainstone *et al*⁵⁸ reported a significant negative correlation between tear volume and staining, whereas others found none.^{57,60} No significant correlations were found between tear volume and ocular surface staining in this study. However, this might be due to the severity of the dry eye groups in the other studies. The frequency of dry eye symptoms in the cohort observed in this study was measured by use of the OSDI, a 12-item patient-reported outcome questionnaire designed to quantify ocular disability due to dry eye disease. Subjects evaluated in this study represent mild-to-moderate dry eye rather than severe dry eye.^{61,62}

No correlations between dry eye symptoms and conjunctival and corneal staining, as well as bulbar and limbal hyperaemia, were observed in this cohort of marginal dry eye patients. These findings are in accordance with current literature, where the poor relationships between ocular signs and dry eye symptoms are criticised.^{8–11,19} However, the use of a composite index might have shown a stronger relationship between staining and dry eye severity, as reported by Sullivan *et al*.⁶³ The classic tests TMH, NIBUT, and PRTT, as well as the new LIPCOF (nasal and temporal) and LWE tests were significantly correlated to dry eye symptoms (Table 2), although these correlations varied in their strengths. The relationship between LWE and dry eye symptoms investigated in this study confirms the findings of Korb *et al*,¹⁵ where LWE was reported to correlate to symptoms as determined by the total Standard Patient Evaluation of Eye Dryness (SPEED) score. LIPCOF has been shown to relate to dry eye symptoms in experienced contact lens wearers¹⁹ as well as naive contact lens wearers,¹³ and this study strengthens the usefulness of LIPCOF in non-contact lens wearers as well.

The predictive ability of the evaluated tests to distinguish between those subjects classified as having dry eye (OSDI score ≥ 15 , OSDI+) and those classified as non-dry eye (OSDI–) was analysed by ROC. In a ROC curve, the true positive rate (sensitivity) is plotted as a function of the false positive rate (1-specificity) for different cut-off points of a parameter. The resulting AUC is a measure of how well a parameter can distinguish between two diagnostic groups (OSDI+ / OSDI–). In addition to the AUC, the corresponding *P*-value indicates if the AUC is significant larger than an AUC of 0.5 (no discrimination). If the *P*-value is lower than 0.05 then it can be concluded that the AUC is significantly different from 0.5 and, therefore, there is evidence that the test has an ability to distinguish between the two subject groups. Classification of AUC is reported as: 0.5 indicates no discrimination, between 0.7 and 0.8 indicates acceptable discrimination, >0.8 indicates excellent discrimination and >0.9 outstanding discrimination.⁶⁴ According to this classification, NIBUT, nasal LIPCOF, and LIPCOF Sum were excellent discriminators, and TMH, PRTT, temporal LIPCOF, and LWE were acceptable discriminators. These results are not surprising, since NIBUT,^{13,65} TMH,^{58,66} PRTT,^{46,47} LIPCOF,^{13,16,18,19} and LWE^{15,18,19} are accepted tests in dry eye assessment. Even though bulbar hyperaemia approached significance (*P* = 0.055), its AUC was too small to be a predictive discriminator. All other tests were not able to discriminate between symptomatics and asymptomatics (OSDI+ / –). This is in accordance with clinical experience and the published

literature, where ocular signs like conjunctival and corneal staining or ocular hyperaemia are found to have a poor ability to detect dry eye in mild to moderate cases.^{2,9,10,14,57,67,68}

Using a combination of tests has been recommended to improve the predictive ability for dry eye.^{9,12–14,63} However, there is no agreement on which tests should be combined and, to our knowledge, it was unknown before this study whether LWE and LIPCOF would be able to help such a combination of tests in non-contact lens wearers. Since a combination of LIPCOF Sum and NIBUT showed an improved predictive ability for later contact lens related dry eye symptoms in naive contact lens wearers,¹³ a comparable combination appeared to be obvious in non-contact lens wearers. The best test combination was calculated by logistic regression analysis (forward: LR), where each variable was automatically added until best predictive ability of OSDI + / – was achieved. This analysis resulted in a formula, combining NIBUT with nasal LIPCOF, which gave an outstanding⁶⁴ discrimination of OSDI + / –.

It is somewhat surprising that temporal LIPCOF was excluded by this analysis. Previous work demonstrated an association between temporal LIPCOF and an objective SICCA score in dry eye patients¹⁶ and prior findings of our group have indicated the usefulness of both nasal LIPCOF and temporal LIPCOF as notable tests in lens wearers.^{13,18,19} Höh *et al*¹⁶ reported significantly increased temporal LIPCOF grades in dry eye patients, although no relationship between nasal LIPCOF and dry eye was found in their study. However, in this study, we classified LIPCOF using an optimised grading scale,^{13,17–19} rather than the ‘LIPCOF score’ published by Höh *et al*,¹⁶ which evaluated the height of the set of folds in comparison to the tear meniscus height.^{16,69} Previous findings of our group suggested an improvement of the predictive ability of LIPCOF using a new classification,^{13,17} where the LIPCOF score is not derived from the height of the folds, but from the number of lid-parallel conjunctival folds that accumulate one above the other.¹⁷

This optimised LIPCOF score enhanced the evaluation of both temporal and nasal LIPCOF, but nasal LIPCOF performed better than temporal LIPCOF and even LIPCOF Sum. Even though the correlations between LIPCOF (temporal, nasal, Sum) and OSDI scores were moderate only, LIPCOF was a good discriminator between normal and mild dry eyes, especially nasal LIPCOF. The results suggest the importance of preferentially evaluating nasal LIPCOF—not only temporal LIPCOF¹⁶—in dry eye assessment in clinical practice. A combination of nasal LIPCOF and NIBUT might be useful as a quick screening test to detect mild dry eye patients in clinical practice.

Conclusions

To our knowledge, this is the first time that the relationships between single dry eye tests and LIPCOF (temporal, nasal, Sum), as well as the ability of LIPCOF to detect dry eye symptoms, analysed by a validated dry eye questionnaire, have been evaluated in a cohort of normal non-contact lens wearers. LIPCOF and LWE were related, as was found in contact lens wearers in a prior investigation,^{18,19} and also related to tear film stability and volume. The tear film tests NIBUT, TMH, and PRIT, as well as the ocular signs LIPCOF and LWE, were significantly increased in symptomatics. The most predictive single tests were NIBUT, nasal LIPCOF, and LIPCOF Sum. A combination of NIBUT and nasal LIPCOF (here named Dry Eye Test Combination (DTC)), showed the best predictive ability of dry eye symptoms in this cohort of non-contact lens wearers. These findings underline the importance of evaluating NIBUT and nasal LIPCOF in the daily clinical routine, even in apparently healthy subjects, to detect mild to moderate dry eye.

Summary

What was known before

- Relations between nasal and temporal lid-parallel conjunctival folds and dry eye symptoms in contact lens wear.

What this study adds

- Relations between nasal and temporal lid-parallel conjunctival folds and dry eye symptoms in non-contact lens wearers. Their predictive ability of dry eye symptoms. Best test combination useful as screening test to detect mild dry eye patients in clinical practice.

Conflict of interest

The authors declare no conflict of interest.

References

- 1 Johnson M. *Dry Eye Questionnaires (PhD Thesis)*. Cardiff University: Cardiff, 2005.
- 2 Srinivasan S, Jones L, Joyce E, Simpson T, Senchyna M. Clinical signs and symptoms in postmenopausal females with and without symptoms of dry eye. *Invest Ophthalmol Vis Sci* 2006; **47**: ARVO E-Abstract: 249.
- 3 Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol* 2000; **118**: 615–621.
- 4 Begley CG, Caffery B, Chalmers RL, Mitchell GL. Use of the dry eye questionnaire to measure symptoms of ocular irritation in patients with aqueous tear deficient dry eye. *Cornea* 2002; **21**: 664–670.

- 5 Nichols KK, Nichols JJ, Mitchell G, Lynn M. The reliability and validity of McMonnies dry eye index. *Cornea* 2004; **23**(4): 365–371.
- 6 Pflugfelder SC. Prevalence, burden, and pharmacoconomics of dry eye disease. *Am J Manag Care* 2008; **14**: S102–S106.
- 7 Smith JA, Albeitz J, Begley C, Caffery B, Nichols K, Schaumberg D *et al*. The epidemiology of dry eye disease: Report of the Epidemiology Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf* 2007; **5**: 93–107.
- 8 Narayanan S, Miller WL, Prager TC, Jackson JA, Leach NE, McDermott AM *et al*. The diagnosis and characteristics of moderate dry eye in non-contact lens wearers. *Eye Contact Lens: Science & Clinical Practice* 2005; **31**: 96–104.
- 9 Bron AJ. Diagnosis of dry eye. *Surv Ophthalmol* 2001; **45**(Suppl 2): S221–S226.
- 10 Nichols KK, Nichols JJ, Mitchell GL. The lack of association between signs and symptoms in patients with dry eye disease. *Cornea* 2004; **23**: 762–770.
- 11 Turner AW, Layton CJ, Bron AJ. Survey of eye practitioners' attitudes towards diagnostic tests and therapies for dry eye disease. *Clin Experiment Ophthalmol* 2005; **33**: 351–355.
- 12 Korb DR. Survey of preferred tests for diagnosis of the tear film and dry eye. *Cornea* 2000; **19**: 483–486.
- 13 Pult H, Murphy PJ, Purslow C. A novel method to predict dry eye symptoms in new contact lens wearers. *Optom Vis Sci* 2009; **86**: E1042–E1050.
- 14 Johnson ME. The association between symptoms of discomfort and signs in dry eye. *Ocul Surf* 2009; **7**: 199–211.
- 15 Korb DR, Herman JP, Greiner JV, Scaffidi RC, Finnemore VM, Exford JM *et al*. Lid wiper epitheliopathy and dry eye symptoms. *Eye Contact Lens* 2005; **31**: 2–8.
- 16 Höh H, Schirra F, Kienecker C, Ruprecht KW. Lid-parallel conjunctival folds are a sure diagnostic sign of dry eye. *Ophthalmologie* 1995; **92**: 802–808.
- 17 Pult H. *The Predictive Ability of Clinical Tests for Dry Eye in Contact Lens Wear (PhD Thesis)*. Cardiff University: Cardiff, 2008.
- 18 Berry M, Pult H, Purslow C, Murphy PJ. Mucins and ocular signs in symptomatic and asymptomatic contact lens wear. *Optom Vis Sci* 2008; **85**: E930–E938.
- 19 Pult H, Purslow C, Berry M, Murphy PJ. Clinical tests for successful contact lens wear: relationship and predictive potential. *Optom Vis Sci* 2008; **85**: E924–E929.
- 20 Korb DR, Greiner JV, Herman JP, Hebert E, Finnemore VM, Exford JM *et al*. Lid-wiper epitheliopathy and dry-eye symptoms in contact lens wearers. *CLAO J* 2002; **28**: 211–216.
- 21 Hughes W. Conjunctivochalasis. *Am J Ophthalmol* 1942; **25**: 48–51.
- 22 de Almeida SF, de Sousa LB, Vieira LA, Chiamollera MI, Barros Jde N. Clinic-cytologic study of conjunctivochalasis and its relation to thyroid autoimmune diseases: prospective cohort study. *Cornea* 2006; **25**: 789–793.
- 23 Di Pascuale MA, Espana EM, Kawakita T, Tseng SC. Clinical characteristics of conjunctivochalasis with or without aqueous tear deficiency. *Br J Ophthalmol* 2004; **88**: 388–392.
- 24 Francis IC, Chan DG, Kim P, Wilcsek G, Filipic M, Yong J *et al*. Case-controlled clinical and histopathological study of conjunctivochalasis. *Br J Ophthalmol* 2005; **89**: 302–305.
- 25 Hirofani Y, Yokoi N, Komuro A, Kinoshita S. Age-related changes in the mucocutaneous junction and the conjunctivochalasis in the lower lid margins. *Nippon Ganka Gakkai Zasshi—Acta Societatis Ophthalmologicae Japonicae* 2003; **107**: 363–368.
- 26 Liu D. Conjunctivochalasis. A cause of tearing and its management. *Ophthalm Plast Reconstr Surg* 1986; **2**: 25–28.
- 27 Meller D, Tseng SC. Conjunctivochalasis: literature review and possible pathophysiology. *Surv Ophthalmol* 1998; **43**: 225–232.
- 28 Mimura T, Usui T, Yamamoto H, Yamagami S, Funatsu H, Noma H *et al*. Conjunctivochalasis and Contact Lenses. *Am J Ophthalmol* 2009; **148**: 20–25.
- 29 Otaka I, Kyu N. A new surgical technique for management of conjunctivochalasis. *Am J Ophthalmol* 2000; **129**: 385–387.
- 30 Wang Y, Dogru M, Matsumoto Y, Ward SK, Ayako I, Hu Y *et al*. The impact of nasal conjunctivochalasis on tear functions and ocular surface findings. *Am J Ophthalmol* 2007; **144**: 930–937 e1.
- 31 Watanabe A, Yokoi N, Kinoshita S, Hino Y, Tsuchihashi Y. Clinicopathologic study of conjunctivochalasis. *Cornea* 2004; **23**: 294–298.
- 32 Yokoi N, Komuro A, Maruyama K, Tsuzuki M, Miyajima S, Kinoshita S. New surgical treatment for superior limbic keratoconjunctivitis and its association with conjunctivochalasis. *Am J Ophthalmol* 2003; **135**: 303–308.
- 33 Yokoi N, Komuro A, Sugita J, Nakamura Y, Kinoshita S. Surgical reconstruction of the tear meniscus at the lower lid margin for treatment of conjunctivochalasis. *Adv Exp Med Biol* 2002; **506**: 1263–1268.
- 34 Yokoi NMDP, Komuro AMDP, Nishii MMD, Inagaki KMD, Tanioka HMS, Kawasaki SMDP *et al*. Clinical impact of conjunctivochalasis on the ocular surface. *Cornea* 2005; **24**(8 Suppl): S24–S31.
- 35 Zhang M, Chen JQ, Liu ZG, Lou LH, Xiao QG, Yao Y *et al*. Clinical characteristics of patients with dry eye syndrome. *Chung-Hua Yen Ko Tsa Chih (Chinese Journal of Ophthalmology)* 2003; **39**: 5–9.
- 36 Zhang XR, Cai RX, Wang BH, Li QS, Liu YX, Xu Y. The analysis of histopathology of conjunctivochalasi. *Chung-Hua Yen Ko Tsa Chih [Chinese Journal of Ophthalmology]* 2004; **40**: 37–39.
- 37 Guillon JP. Use of the tearscope plus and attachments in the routine examination of the marginal dry eye contact lens patient. *Adv Exp Med Biol* 1998; **438**: 859–867.
- 38 Dundas M, Walker A, Woods RL. Clinical grading of corneal staining of non-contact lens wearers. *Ophthalmic Physiol Opt* 2001; **21**: 30–35.
- 39 Murphy PJ, Lau JS, Sim MM, Woods RL. How red is a white eye? Clinical grading of normal conjunctival hyperaemia. *Eye* 2007; **21**: 633–638.
- 40 Bailey IL, Bullimore MA, Raasch TW, Taylor HR. Clinical grading and the effects of scaling. *Invest Ophthalmol Vis Sci* 1991; **32**: 422–432.
- 41 Santodomingo-Rubido J, Wolffsohn J, Gilmartin B. Conjunctival epithelial flaps with 18 months of silicone hydrogel contact lens wear. *Eye Contact Lens* 2008; **34**: 35–38.
- 42 Markoulli M, Carnt N, Jalbert I, Keay L, Naduvilath T, Papas E. Resolution and clinical characteristics of conjunctival 'Flaps'. *Invest Ophthalmol Vis Sci* 2007; **48**: ARVO E-Abstract: 5391.
- 43 Thota S, Perrigin J, Miller W, Leach N, Bergmanson J, Back A. Conjunctival flaps in silicone hydrogel lens wearers. *Invest Ophthalmol Vis Sci* 2006; **47**: ARVO E-Abstract: 82.
- 44 Graham AD, Truong TN, Lin MC. Conjunctival epithelial flap in continuous contact lens wear. *Optom Vis Sci* 2009; **86**: e324–e331.

- 45 Pult H. Digital analyzes of lid parallel conjunctival folds. In: *Optometry and Vision Research: Contact'10*; Wolfsburg, Germany; 15–17 October 2010.
- 46 Hamano H, Hori M, Hamano T, Mitsunaga S, Maeshima J, Kojima S *et al*. A new method for measuring tears. *CLAO J* 1983; **9**: 281–289.
- 47 Patel S, Farrell J, Blades KJ, Grierson DJ. The value of a phenol red impregnated thread for differentiating between the aqueous and non-aqueous deficient dry eye. *Ophthalmic Physiol Opt* 1998; **18**: 471–476.
- 48 Korb DR, Herman JP, Solomon JD, Greiner JV, Blackie CA. Lid wiper staining and sequential fluorescein instillation. *Invest Ophthalmol Vis Sci* 2006; **47**: ARVO E-Abstract: 242.
- 49 Michel M, Sickenberger W, Pult H. The effectiveness of questionnaires in the determination of contact lens induced dry eye. *Ophthalmic Physiol Opt* 2009; **29**: 479–486.
- 50 Pult H, Murphy PJ, Purslow C, Nyman J, Woods RL. Limbal and bulbar hyperaemia in normal eyes. *Ophthalmic Physiol Opt* 2008; **28**: 13–20.
- 51 Josephson JE, Caffery BE. Corneal staining characteristics after sequential instillations of fluorescein. *Optom Vis Sci* 1992; **69**: 570–573.
- 52 Korb DR, Korb JM. Corneal staining prior to contact lens wearing. *J Am Optom Assoc* 1970; **41**: 228–232.
- 53 Albiets JM. Prevalence of dry eye subtypes in clinical optometry practice. *Optom Vis Sci* 2000; **77**: 357–363.
- 54 Moss SE, Klein R, Klein BEK. Prevalence of and risk factors for dry eye syndrome. *Arch Ophthalmol* 2000; **118**: 1264–1268.
- 55 Ehlers N. The precorneal film. Biomicroscopical, histological and chemical investigations. *Acta Ophthalmol Suppl* 1965; (SUPPL 81): 1–134.
- 56 Patel S, Wallace I. Tear meniscus height, lower punctum lacrimale, and the tear lipid layer in normal aging. *Optom Vis Sci* 2006; **83**: 731–739.
- 57 Nichols KK, Nichols JJ, Lynn Mitchell G. The relation between tear film tests in patients with dry eye disease. *Ophthalmic Physiol Opt* 2003; **23**: 553–560.
- 58 Mainstone JC, Bruce AS, Golding TR. Tear meniscus measurement in the diagnosis of dry eye. *Curr Eye Res* 1996; **15**: 653–661.
- 59 Golding TR, Bruce AS, Mainstone JC. Relationship between tear-meniscus parameters and tear-film breakup. *Cornea* 1997; **16**: 649–661.
- 60 Savini G, Barboni P, Zanini M. Tear meniscus evaluation by optical coherence tomography. *Ophthalm Surg Lasers Imaging* 2006; **37**: 112–118.
- 61 Miller KL, Walt JG, Mink DR, Satram-Hoang S, Wilson SE, Perry HD *et al*. Minimal clinically important difference for the ocular surface disease index. *Arch Ophthalmol* 2010; **128**: 94–101.
- 62 Walt J In: *Ocular Surface Disease Index (OSDI) Administration and Scoring Manual*. Allergan, Inc: Irvine, CA, 2004.
- 63 Sullivan BD, Whitmer D, Nichols KK, Tomlinson A, Foulks GN, Geerling G *et al*. An objective approach to dry eye disease severity. *Invest Ophthalmol Vis Sci* 2010; **51**(12): 6125–6130.
- 64 Hosmer DW, Lemeshow S. *Applied Logistic Regression*. John Wiley & Sons Incorporated: New York, USA, 2000.
- 65 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.
- 66 Kawai M, Yamada M, Kawashima M, Inoue M, Goto E, Mashima Y *et al*. Quantitative evaluation of tear meniscus height from fluorescein photographs. *Cornea* 2007; **26**: 403–406.
- 67 Nichols KK, Mitchell GL, Zadnik K. The repeatability of clinical measurements of dry eye. *Cornea* 2004; **23**: 272–285.
- 68 Kaercher T, Bron AJ. Classification and diagnosis of dry eye. *Dev Ophthalmol* 2008; **41**: 36–53.
- 69 Schirra F, Hoh H, Kienecker C, Ruprecht KW. Using LIPCOF (lid-parallel conjunctival fold) for assessing the degree of dry eye, it is essential to observe the exact position of that specific fold. *Adv Exp Med Biol* 1998; **438**: 853–858.
- 70 Kurihashi K, Yanagihara N, Honda Y. A modified Schirmer test: the fine-thread method for measuring lacrimation. *J Pediatr Ophthalmol* 1977; **14**: 390–397.