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Lid-parallel conjunctival folds (LIPCOF) and dry eye: a multicentre study

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ABSTRACT

Aims The study was designed to test the clinical application of the grading of lid-parallel conjunctival folds (LIPCOF) as a diagnostic test for dry eye.

Methods At 12 centres in 11 countries, 272 eyes of 272 dry eye patients (75 men, 197 women) were examined. Their mean age was 52.7±16.2 years. The LIPCOF were graded according to the method of Höh *et al.* The tear film break-up time (BUT) was measured, and fluorescein staining and the Schirmer 1 test were performed. The subjective symptoms were evaluated by 16 questions.

Results The LIPCOF score demonstrated significant positive correlations with age, dry eye disease severity and fluorescein staining ($r>0.2$, $p<0.001$), and negative correlations with BUT and results of the Schirmer 1 test ($r<-0.2$, $p<0.001$). The LIPCOF score exhibited a significant correlation with the overall subjective symptoms ($r=0.250$, $p<0.001$). The sensitivity and specificity of LIPCOF grading for discriminating between normal and dry eyes were best with the cut-off between LIPCOF degrees 1 and 2.

Conclusions The displayed medium sensitivity and specificity, and good positive predictive value of the LIPCOF test support the use of LIPCOF grading as a simple, quick and non-invasive dry eye screening tool.

INTRODUCTION

The prevalence of dry eye symptoms in adults is reported to be 5%–30%.[1] Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance and tear film instability with potential damage to the ocular surface.[1] It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.[1] The diagnosis of dry eye disease is based on subjective symptoms, objective clinical signs and diagnostic tests. Several clinical diagnostic tests are used in clinical and research practice, but the correlations between their results are weak.[2–4]

The first report of conjunctivochalasis was published in 1835 by Middlemore,[5] without any clinical grading. Classifications of the folds in conjunctivochalasis (as a sign of dry eye syndrome) from different standpoints were subsequently proposed by several research groups.[5–10] The most widely used grading of conjunctivochalasis is the lid-parallel conjunctival folds (LIPCOF) scheme of Höh *et al*, which is reported to be a simple, non-invasive diagnostic test for dry eye diseases.[6–8 11–15] During slit lamp examination, it is easy to detect and grade the LIPCOF bordering the posterior lid margin. Claims for the applicability of the LIPCOF test are based on the results of a single research group of Höh,[6–8] and its suitability has been questioned in several reports.[9 16] Therefore, it is essential to evaluate the appropriateness of this test in an independent, multicentre study.

Accordingly, the aim of the present study was to determine the correlations between the LIPCOF's degrees and clinical signs, the results of classical dry eye disease tests and subjective symptoms in dry eye patients.

MATERIALS AND METHODS

In total, the data of 272 eyes of 272 dry eye patients from general ophthalmology clinics, who were treated or were intended to be treated due to their typical dry eye complaints, clinical signs and clinical tests (mean age: 52.7 years, SD: 16.2 years; 75 men and 197 women), were included in the analysis. The prospective study was conducted at 12 centres in 11 countries (two centres in Hungary and one centre each in Belarus, Bulgaria, Croatia, Czech Republic, Egypt, Lebanon, Poland, Slovakia, Slovenia, and Turkey). The data of patients with dry eye symptoms ranging from mild to more severe dry eye disease were included in each institute. For each patient, all examinations (LIPCOF, other tests and the questionnaire) were performed on the same day. Patients with additional ocular surface diseases other than dry eye or who had previously undergone ophthalmic surgery or worn contact lenses in the preceding months were excluded. All subjects were examined in accordance with the tenets of the Helsinki Declaration. The examination protocol was approved by the Regional and Institutional Ethics Committee, Budapest, Hungary.

The LIPCOFs were graded by means of slit lamp examination, using the method described by Höh *et al*.[6–8] The patient was asked to blink several times in the primary position of the gaze. The examiner looked for a horizontal conjunctival fold at the transition zone from the middle to the temporal third of the lower eyelid, with the slit lamp adjusted to furnish the brightness and magnification for a panoramic view. The degrees are according to the size of the conjunctival folds as compared with the height of the normal tear meniscus height and to the number of individual folds they comprise. Degree 0: no permanently present fold; degree 1: where a single small fold in the primary eye position appears smaller than the

normal tear film meniscus; degree 2: multiple folds up to the height of normal tear meniscus; and degree 3: multiple folds higher than the normal tear meniscus. Real LIPCOFs disappear when the observer pulls the lower eye lid away from the eye. They form again after some blinks, and they always form in the same stage.

After vital staining of the ocular surface with fluorescein, the corneal and bulbar conjunctival staining and tear film break-up time (BUT) were measured, and then the Schirmer 1 test (without ocular surface anaesthesia and for 5 min) was performed.[17 18]

The subjective complaints and symptoms were evaluated with 16 language-validated questions. The questions were adopted from the questionnaire of the External Eye Disease Group and other validated questionnaires (appendix 1).[1 18] The original language of the questions was English, and they were translated into each local language and tested by healthy unbiased native speakers.

Even if the degree of dry eye had been established in previous visits, the diagnosis and grading were repeated via fluorescein staining, fluorescein BUT measurement, the Schirmer 1 test and the severity score were documented in the data collection sheet. For fluorescein staining and grading over the cornea, temporal and nasal conjunctiva were assessed (0=no staining, 1=a few staining points, 2=medium staining, and 3=severe staining, with a maximum of three points at each of the three locations, for an overall maximum of nine points); with regard to the different degrees of staining: 1–3 points=mild, 4–6 points=moderate, and 7–9 points=severe dry eye disease. For the fluorescein BUT measurement, a BUT of >7 s=mild, 4–7 s=moderate, and 0–3 s=severe dry eye disease. The results of the Schirmer 1 test: >7 mm=mild, 4–7 mm=moderate, and 0–3 mm=severe dry eye disease. In all tests, mild, moderate and severe dry eye disease was awarded a score of 1, 2 and 3, respectively. The values were summarised and the overall severity score was categorised as follows: <5=grade 1 (mild), 5–7=grade 2 (moderate) and 8–9=grade 3 (severe).

Finally, for determination of the sensitivity and specificity of the LIPCOF grading, a healthy control group was recruited with the same age and gender distribution as the dry eye patients mentioned above. The control group consisted of 140 eyes of 140 healthy subjects (mean age: 50.3 years, SD: 14.5 years; 48 men and 92 women). The inclusion criteria were: no subjective dry eye symptoms, no current dry eye treatment, no other ocular surface disease and no contact lens wear. Their dry eye test values were required to be normal : Schirmer 1 test: >10 mm/5 min; BUT >10 s; ocular surface staining <4 points (in a nine-point scale). The LIPCOF sensitivity and specificity to distinguish between normal and dry eyes were calculated for each possible LIPCOF cut-off point, for example, 0–1, 1–2 and 2–3.

For statistical analysis, the right eye of the patients and controls were included if both eyes were eligible. The correlations between the LIPCOF degree and the results of other diagnostic tests or the subjective symptoms were analysed with the Kendall-tau test. The differences between each subgroup of different LIPCOF degrees were checked by means of the Kruskal-Wallis test, and post hoc pairwise comparisons were made with the Mann-Whitney test. Treated and untreated subgroups, as well as aqueous tear-deficient dry eye (ADDE, Schirmer 1 test value≤10 mm/5 min) and non-aqueous tear-deficient dry eye (NADDE) subgroups were compared using the binomial, χ^2 and Mann-Whitney tests. A level of $p<0.05$ was considered to indicate a statistically significant difference in the Kendall-tau and Kruskal-Wallis tests, and the Bonferroni correction was applied in the Mann-Whitney test. Statistical analysis was carried out with SPSS for Windows, V.15.0 (SPSS, Inc., Chicago, Illinois, USA).

Table 1 Demographic data on the patients and the test results in untreated and treated subgroups and in the overall patient population

Parameter	Untreated (A) (number or mean±SD)	Treated (B) (number or mean±SD)	Overall (number or mean±SD)	Statistical difference (p value) A versus B
Number of subjects	128	144	272	0.363*
Sex (men/women)	42/86	33/111	75/197	0.068†
Age (years)	53.9±16.4	51.6±15.9	52.7±16.2	0.269‡
Severity scale (grade 1/grade 2/ grade 3)	85/31/12	55/51/38	140/82/50	<0.001†
Complaints Q3, 4, 7, 10, 12 (points)	5.10±2.89	7.31±2.96	6.27±3.12	<0.001‡
Fluorescein staining (points)	1.14±2.05	2.84±5.61	2.04±4.39	<0.001‡
Break-up time (sec)	8.08±5.01	6.78±4.55	7.39±4.81	0.010‡
Schirmer 1 test (mm/5 min)	10.57±7.71	9.13±6.81	9.81±7.27	0.136‡
Lid-parallel conjunctival folds (degree 0/degree 1/ degree 2/degree 3)	16/45/39/28	25/52/36/31	41/97/75/59	0.611†

*Binomial test.
†χ^2 test.
‡Mann-Whitney test.

RESULTS

The demographic data and the means and SDs of the various test results are presented in tables 1 and 2. The data on the untreated and treated subgroups differed statistically in several respects (table 1). In the treated subgroup, the severity grades

Table 2 Demographic data on the patients and the test results in aqueous tear-deficient dry eye (ADDE) and non-aqueous tear-deficient dry eye (NADDE) subgroups

Parameter	ADDE (C) (number or mean±SD)	NADDE (D) (number or mean±SD)	Statistical difference (p value) C versus D
Number of subjects	162	108	0.001*
Sex (men/women)	41/119	31/75	0.515†
Age (years)	53.90±15.79	50.84±16.72	0.126‡
Severity scale (grade 1/ grade 2/grade 3)	60/58/44	78/24/6	<0.001†
Complaints Q3, 4, 7, 10, 12 (points)	6.83±3.25	5.44±2.76	0.001‡
Fluorescein staining (points)	2.70±5.36	1.09±2.00	<0.001‡
Break-up time (sec)	6.37±4.68	8.91±4.65	<0.001‡
Schirmer 1 test (mm/ 5 min)	5.29±3.21	16.59±6.32	<0.001‡
Lid-parallel conjunctival folds (degree 0/degree 1/ degree 2/degree 3)	18/45/51/48	22/52/23/11	<0.001†

*Binomial test.
†χ^2 test.
‡Mann-Whitney test.

Table 3 Correlations of lid-parallel conjunctival folds degrees with other parameters in the untreated and treated subgroups and in the overall patient population

	Untreated (n=128)		Treated (n=144)		Overall (n=272)	
Parameter	**R**	**P**	**r**	**p**	**r**	**p**
Age	0.168	0.013	0.255	<0.001	0.219	<0.001
Severity	0.367	<0.001	0.484	<0.001	0.403	<0.001
Complaints Q3, 4, 7, 10, 12	0.200	0.004	0.405	<0.001	0.277	<0.001
Fluorescein staining	0.191	0.012	0.299	<0.001	0.227	<0.001
Break-up time	−0.173	0.012	−0.299	<0.001	−0.232	<0.001
Schirmer 1 test	−0.260	<0.001	−0.276	<0.001	−0.261	<0.001

were more severe, and the patients had more complaints than in the untreated subgroup. The fluorescein staining of the ocular surface was more severe, and the BUT was shorter in the treated subgroup than in the untreated one. However, the numbers of subjects, sex ratios, ages, Schirmer wetting and LIPCOF degrees were similar in the two subgroups.

Among the eyes in the analysis, the Schirmer 1 test value was equal to or less than 10 mm/5 min in 162 eyes (ADDE subgroup, see table 2). The data on the ADDE and NADDE subgroups differed statistically in several respects: the disease severity, scale and the complaints were more pronounced, and the fluorescein staining, the BUT and the Schirmer 1 tests were more pathological in ADDE than in the NADDE subgroup. More severe LIPCOF degrees (2 and 3) were also more frequent in the ADDE subgroup, while less severe degrees (0 and 1) were typical in the NADDE subgroup (p=0.0001; table 2).

The LIPCOF degree exhibited significant positive correlations with age, severity score and the corneal fluorescein staining, and significant negative correlations with the tear film, BUT and results of the Schirmer 1 test in both the untreated and treated subgroups, as well as in the overall group, but the correlations were stronger in the treated subgroup (table 3). The correlations in the ADDE and NADDE subgroups were also similar, however, the age and Schirmer 1 test value exhibited no correlation with LIPCOF degree in the NADDE subgroup (table 4).

Only the age of patients with LIPCOF degree 3 proved to be significantly higher than those of the other LIPCOF grade subgroups (figure 1). The higher the LIPCOF degree, the more severe the subjective symptoms (figure 2). The tear film BUTs were similar in LIPCOF degrees 0 and 1, but were significantly shorter in the higher LIPCOF grades (figure 3). Similarly, the Schirmer 1 test results were the same in LIPCOF degrees 0 and 1, but were significantly lower in LIPCOF degrees 2 and 3 (figure 4).

Table 4 Correlations of lid-parallel conjunctival folds degree with other parameters in aqueous tear-deficient dry eye (ADDE) and non-aqueous tear-deficient dry eye (NADDE) subgroups

	ADDE (n=162)		NADDE (n=108)	
Parameter	**R**	**p**	**r**	**p**
Age	0.264	0.000	0.119	0.110
Severity	0.308	0.000	0.438	0.000
Complaints Q3, 4, 7, 10, 12	0.212	0.001	0.314	0.000
Fluorescein staining	0.164	0.011	0.225	0.007
Break-up time	−0.156	0.011	−0.257	0.001
Schirmer 1 test	−0.257	0.001	0.022	0.775

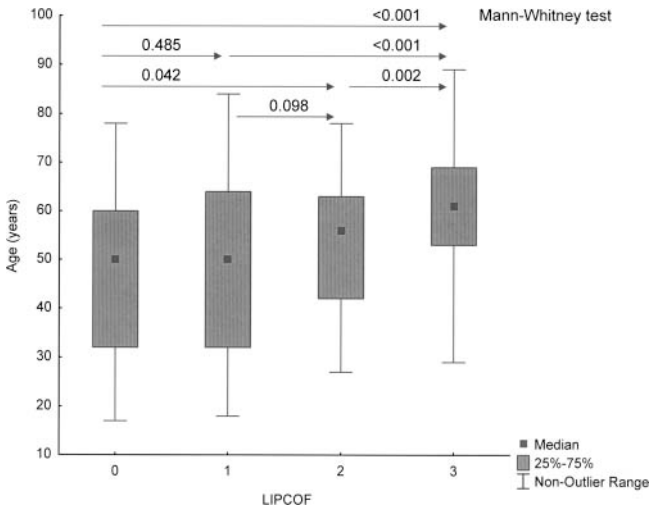

Figure 1 Median age in the four subgroups with different lid-parallel conjunctival folds degrees (Kruskal-Wallis test, $p < 0.001$).

The LIPCOF degree correlated significantly with various subjective symptoms (appendix 2 and tables 3–4). However, there were fewer such correlations with the LIPCOF grade in the untreated subgroup than in the treated subgroup or the overall group.

An attempt was made to find a cut-off point between normal and dry eyes among the different LIPCOF grades. The sensitivities and specificities of the LIPCOF grades for different cut-off points are listed in table 5. There was no significant difference between the sensitivity and specificity parameters in the untreated and treated subgroups (table 5).

DISCUSSION

In the present multicentre observational clinical study, significant correlations were found between the LIPCOF grade and subjective and objective signs of dry eye in patients with different degrees of severity of dry eye disease, including untreated and treated patients, and also the ADDE and NADDE subgroups. The higher the LIPCOF degree, the more severe the subjective complaints, and the worse the dry eye test results.

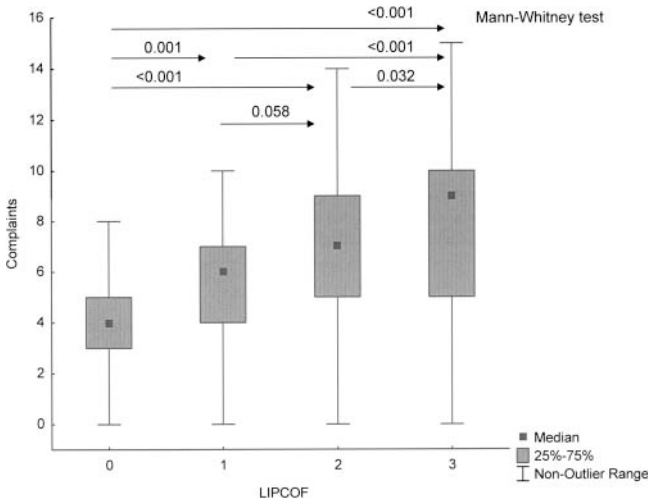

Figure 2 Complaints in different lid-parallel conjunctival folds degrees (Kruskal-Wallis test, $p < 0.001$).

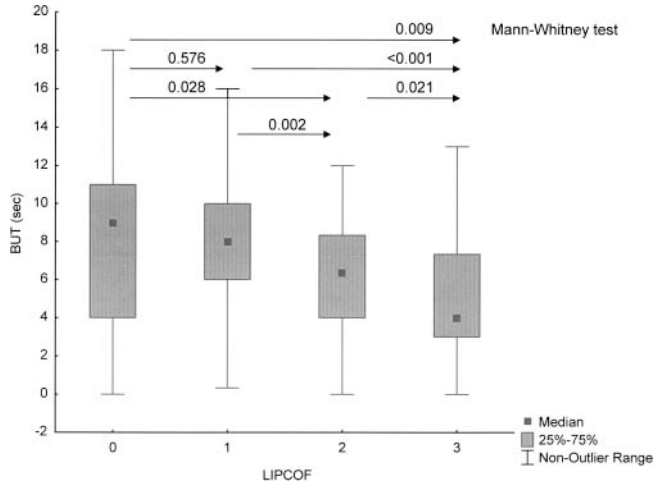

Figure 3 Break-up times in different lid-parallel conjunctival folds degrees (Kruskal-Wallis test, $p < 0.001$).

The degree of LIPCOF intensity was significantly higher with advancing age. In their large population-based study, Zhang *et al*[19] also found that the prevalence rate of more severe conjunctival folds (grades II and III) increased with age, while the prevalence of the lowest grade (grade I) decreased. Murube[5] discussed several theories relating to the aetiology and pathology of the folds as related to senile degeneration of the subconjunctival tissue. The correlation of the LIPCOF grades with age might be due to this senile degeneration, and might be related to the fact that dry eye disease is more frequent in older age groups. However, Höh *et al*[6] found that the LIPCOF grade was independent of age and gender in their sample of 267 volunteers, possibly due to the different patients selection criteria.

Weak, but significant correlations, were found between the LIPCOF degree and the subjective dry eye complaints. Boldt and Höh[12] and Pult *et al*[20] also reported a significant correlation between the LIPCOF grade and the subjective complaints of dry eye disease. However, Sickenberger *et al*[15] observed a significant disagreement between the LIPCOF grade and the subjective dryness and comfort grade in 91 volunteers ($p < 0.01$) who were contact lens wearers.

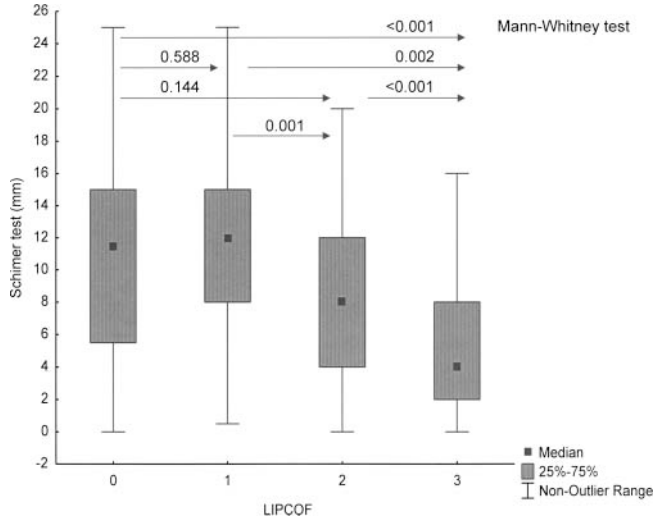

Figure 4 Schirmer 1 test results in different lid-parallel conjunctival folds degrees (Kruskal-Wallis test, $p < 0.001$).

The correlations between the LIPCOF degree and the results of other diagnostic tests were similarly low as in the case of the intercorrelations of the classical diagnostic dry eye tests.[2–4 20] Data from previous studies and our own experience indicate that these relatively low correlations are common, because different diagnostic tests reflect different and relatively independent anatomic, physiological or pathological aspects of the tear film and the ocular surface. The tests can also furnish varying results in dry eye disease in different subjects and in the same patient at different times. We therefore suggest that the low level of correlations between the results of various diagnostic tests reflects not the unsuitability of the individual test, but rather the multiaetiological nature and diverse pathophysiological mechanisms involved in the complex phenomenon of dry eye disease.

A potential weakness of this study is that the tests were not masked in relation to one another, which might cause bias: some spurious correlations. Our study was performed close to the usual clinical conditions. In standard clinical setting, it is not possible to mask tests in relation to each other, since it would pose unavoidable obstacles: several clinicians examining each patient in close succession with different tests. Masking would also be difficult in this study, since masking the four tests and the questions would necessitate a five-fold increase in the number of participating ophthalmologists in each of the 12 examination sites.

The aetiology and pathomechanism of LIPCOF are so far unexplained, although the connection of conjunctivochalasis with dry eye syndrome is widely acknowledged. Various hypotheses have been postulated concerning the pathogenesis of conjunctivochalasis in the recent past, and the two most popular aetiological theories relate to (1) the breakdown of elastic fibres in the redundant conjunctiva with negligible inflammatory cell infiltration and (2) inflammation of the conjunctiva.[5 9 21] The role of tear deficiency is also confirmed by our present results as we found a negative correlation between Schirmer 1 test value and the LIPCOF degree, and in the ADDE subgroup we found more severe LIPCOF degrees than in the NADDE subgroup.

Concerning the pathomechanism of the tear film instability caused by conjunctivochalasis, the most widely used hypothesis is that the presence of the conjunctival folds can disrupt the lower tear meniscus and cause tear film instability and delayed tear clearance.[5 9] According to this hypothesis, authors considered that the clinically important condition is when the height of the folds reaches the actual meniscus height. This hypothesis was supported by our results, whereas, symptoms of patients with LIPCOF degrees 2 and 3 were more serious compared with those with lower LIPCOF degrees (LIPCOF 0 and 1). This could be the theoretical ground to place the LIPCOF cut-off value between normal and pathologic between degrees 1 and 2.

In our study, the sensitivity and specificity of LIPCOF (independently of the different cut-off points) were weaker than those presented by Höh *et al*.[6] Their results suggested that the LIPCOF grades are a highly reliable indicator of dry eye: in 267 patients, they found a negative predictive value of 75.95% and a positive predictive value 93.09% (with a cut-off point between grades 0 and 1). In our series, the LIPCOF test displayed medium sensitivity and specificity, with good positive and medium negative predictive value, for the diagnosis of dry eye disease with a cut-off point between grades 1 and 2. Pult *et al*[20] found that nasal LIPCOF was one of the best discriminators of the ocular signs, and a combination of nasal LIPCOF

Table 5 Sensitivity and specificity of LIPCOF grading

	Cut-off point between LIPCOF degrees 0 and 1			Cut-off point between LIPCOF degrees 1 and 2			Cut-off point between LIPCOF degrees 2 and 3		
	Untreated versus controls (%)	Treated versus controls (%)	Overall versus controls (%)	Untreated versus controls (%)	Treated versus controls (%)	Overall versus controls (%)	Untreated versus controls (%)	Treated versus controls (%)	Overall versus controls (%)
Sensitivity	87.5	82.6	84.9	52.3	46.5	49.3	21.9	21.5	21.7
Specificity	20.7	20.7	20.7	63.6	63.6	63.6	90.0	90.0	90.0
Accuracy	54.1	51.7	52.8	58.0	55.0	56.4	55.9	55.8	55.8
Positive predictive value	50.2	51.7	67.5	56.8	56.8	72.4	66.7	68.9	80.8
Negative predictive value	64.4	53.7	41.4	59.3	53.6	39.2	55.8	52.7	37.2

LIPCOF, lid-parallel conjunctival folds.

and non-invasive BUT resulted in improved predictability. Erdélyi *et al*[13] also found significantly different LIPCOF grades in healthy subjects as compared with dry eye patients, whereas, Miller *et al*[16] observed only minimal differences in LIPCOF grades between moderate dry eye subjects (n=14) and healthy persons (n=8). In the latter study, the conjunctival folds did not correlate with any of the examined parameters, such as the tear osmolarity, conjunctival bulbar injection or corneal staining. They concluded that LIPCOF grading has no differential diagnostic value. Dausch *et al*[22] and Höh and Schwanengel[23] concluded that in response to dry eye therapy, the LIPCOF parameter improved significantly and can be useful in monitoring dry eye treatments.

It must be emphasised that the present correlation study involved only patients with dry eye symptoms because the aim was to compare the results of different tests for dry eye syndrome, and to examine their correlations in untreated or treated dry eye conditions. In untreated patients, the tests relate to the original disease characteristics, whereas in treated patients, the tests also reflect the effects of treatment. Our results led us to conclude that LIPCOF grading measures the relatively independent aspects of dry eye disease, as it exhibited medium to strong positive and statistically significant correlations with dry eye complaints and disease severity, but weak correlations with other classical dry eye diagnostic tests.[2–4 20] Dry eye is a multifactorial disease with many different subtypes from the aspects of origin and pathomechanism.[24] A good combination of different tests might cover the diagnosis of a larger spectrum of dry eye disease. Future studies should attempt to identify the connections between the aetiological and pathological types of dry eye disease and the LIPCOF grades. High-magnification optical coherence tomography images might help to clarify the morphological aspects of LIPCOF in a more objective way.[25]

In summary, we found that the LIPCOF test exhibited medium sensitivity and specificity with a good positive predictive value for the diagnosis of dry eye disease in both untreated and treated patients. These results lend support to the use of LIPCOF as a clinical screening test. In view of its non-invasive nature and simplicity, we suggest the inclusion of LIPCOF grading as an additional rapid dry eye screening test as part of the everyday ophthalmological clinical routine examination protocol.

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Competing interests None.

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